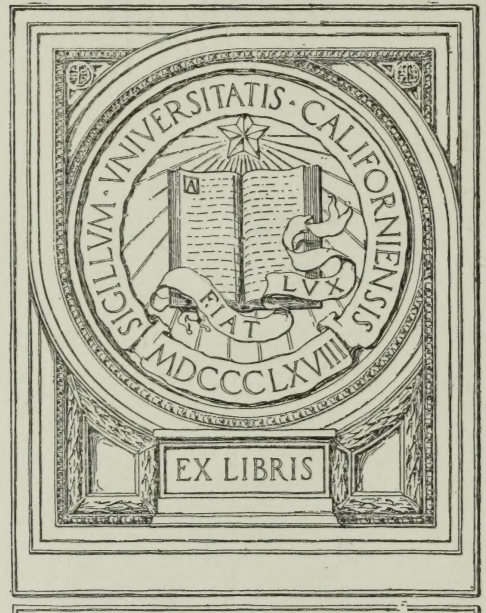
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MODERN MEDICINE

ITS THEORY AND PRACTICE

IN ORIGINAL CONTRIBUTIONS BY AMERICAN AND FOREIGN AUTHORS

EDITED BY

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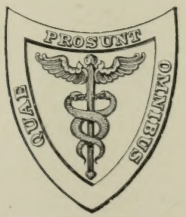
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VOLUME VI

DISEASES OF THE URINARY SYSTEM—DISEASES OF THE DUCTLESS GLANDS—DISEASES OF OBSCURE CAUSATION—DISEASES OF THE MUSCLES—VASOMOTOR AND TROPHIC DISORDERS—LIFE INSURANCE

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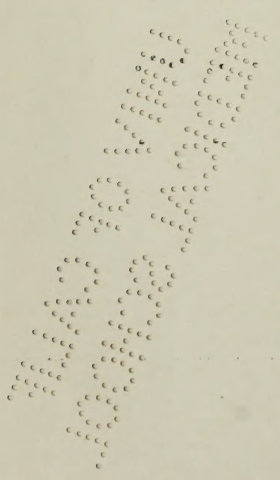


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PART I.

DISEASES OF THE URINARY SYSTEM.

CHAPTER I.

INTRODUCTION TO THE DISEASES OF THE KIDNEY.

By JOHN McCRAE, M.B. (Tor.), M.R.C.P. (Lond.).

It is not the intention of the writer of this article to attempt to put forward anything new, nor yet to give in detail the knowledge that we possess of the physiology or pathology of any particular part of the kidney. So large a task as the latter would naturally fall to other hands. Nevertheless, we are in possession of a certain accumulation of fact and a greater of theory about the functions and the structure of the kidney, and the most that can be attempted in this place is to point out the general trend of these ideas.

Some investigators exalt the glomerulus, others the tubule; some believe that forces, largely mechanical, govern the excretion of urine, others that the vital powers and the selective ability of cells are more potent. While dogmatic assertion is comfortable for the student, it is not quite so just for the advanced reader, and the object here sought is to approach the subject with a mind as open as possible even though the result be that the reader is left with the idea that there is a great deal of uncertainty still prevailing with regard to the processes that go on in the kidney. This is inevitable. In the last twenty-five years there has been a great mass of work done with reference to the problems presented by urinary secretion, and one must admit that there has been no advance made in that time at all commensurate with the energy expended, or at all comparable with the increase of knowledge concerning other apparently less important organs.

THE PHYSIOLOGY OF THE KIDNEY.

Since the days of Bright the importance of the kidney as a seat of disease has certainly not been underestimated, so that there are many diseases with urinary manifestations in which it is difficult to keep the kidney out of the mental picture, innocent though it be. As an excretory organ,

while it probably stands second to the alimentary tract, it certainly surpasses in importance the skin, whose total excretion of water it equals, and it greatly surpasses such subsidiary systems of excretion as the breath and the saliva. With excretion so large and so important, it is natural that it should be held responsible for much that merely goes past its portal; being dependent on other systems to a large extent, the abnormal products appearing in the urine are often not the product of disease of the kidney but of some other organ or system. The true view of diseases of the kidney cannot be attained until we are able rightly to estimate the variations in excretion for which it is *not* responsible. The kidneys excrete and put the finishing touches upon the urinary fluid; they are acting at the end of the metabolic course both as active and as passive agents. There are some modifications of the excreted products over which they have control, and some over which they have none. The limits of such control are what we endeavor to determine by experimental work, and there is at our disposal evidence which tends to show that while to some extent the kidneys are mere mechanical contrivances, mere filters, so to speak, they are to a far greater degree active, specific glands.[1] The daily performance of the healthy kidney is no doubt a combination of these mechanical and vital processes. Yet the more one follows the conflict of evidence and the varying results that have been obtained by the use of similar experiments on kidney functions, the more must it be realized that these functions need not be absolutely hard and fast, unalterable, specific rules of procedure. Compensatory assistance of organ to organ, of one portion of an organ to another, is so widely seen that it is surely a law—and of the working of this law the kidney often avails itself. Glomerular secretion and cellular secretion undoubtedly assist and compensate for one another; and the history of any renal case is the sum total of successes and failures in these adaptations. Nor does it end here; the kidney, as an end link in the vascular chain, is ready at all times to fall back upon the vascular system, and in time of stress throw its burden upon the vessels, which, in turn, seek the help of the adjuvant systems, the alimentary canal, the skin, and the other lesser excretory organs. Witness in nephritis the excretion of urea in the saliva, of chlorides in the fæces. It is obvious that the variations in experimental results, and the difficulty experienced in trying to lay down hard and fast rules as to kidney function arise from this very "give and take" between the different parts of the kidney, and between the kidney and its fellow-organs.

The rules of function that can be fairly considered as settled are these: The glomeruli excrete water and salts, such as sulphates, phosphates, and carbonates, especially when these are in excess; many foreign substances, such as sugar, peptone, egg albumen, and hæmoglobin (Adams Bridges, Adami), if injected, are also excreted by the glomeruli; yet sugar is excreted by the tubules when the kidney is poisoned by phloridzin (Leowi and Schmid), and many pigments, when injected, have been found to be excreted by the tubules (Hober and Konigsberg). Urea is so readily diffusible that it is hard to believe that it is not excreted by the glomeruli, yet urea and uric acid are generally credited to the tubules (Stewart); uric acid, indeed,

[1] The infiltration theory was enunciated by Ludwig, and was supported with modifications by Hans Meyer and Koranyi, while the secretory theory was upheld by Bowman, Heidenhain, and, again, with modifications, by Bartels.

seems to be thrown out by the convoluted tubules and the ascending loop of Henle (Sauer, Anten), while phloridzin, cantharidin, and perhaps mercury are excreted by the tubules (Henderson). Apparent discrepancies as to the place of excretion of any substance arise not from mistaken observations, but because the adaptability of the kidney causes these substances to be excreted now in one way, now in another. There is much reason to suppose that water and salts may be excreted by the tubular epithelium also; in short, it seems as if the tubules can share every glomerular labor when the need arises.

Certain it is that when, by reason of altered blood pressure, the glomeruli cease their activity the tubular epithelium has been proved to take up their function, so that excretion goes on. Nor is this assistance confined to temporary embarrassments of the glomeruli. Müller[1] has pointed out that in a case of diffuse nephritis with œdema and oliguria (which in turn yielded, and polyuria ensued) the convoluted tubules widened and their regenerated epithelium became quite endothelial in type. The evident meaning of this is that these tubules took up, to a greater extent than ever, the work of excreting urinary water; they doubtless lost to some degree the functions that they ordinarily possess, and adapted themselves to their new work, for which their simpler endothelium-like structure fitted them. Müller thinks that this is an explanation, partial, at least, of the power of a kidney deprived of many glomeruli to excrete a vastly increased amount of water. In any case, it is an excellent example of what has been referred to above as the "give and take" of the one part of the kidney and another. Nor is there anything wonderful in this adaptation, for the flattened endothelium-like cells in the dilated tubule have merely asserted their relationship to the flattened epithelial cells covering the glomerular tuft, which normally possess this structure, adapted rather to the excretion of water than to the more elaborate processes which are the duty of the epithelial cell of the tubule.

Nor must we overlook the power possessed by the tubular epithelium of absorption from the fluid in its lumen; that is, there is good reason to suppose that the action of the epithelium is not always supplementary to that of the glomeruli, but may be antagonistic or at least exerted in a contrary direction; doubtless absorption back to the blood and lymph of water already secreted by the glomeruli occurs through the tubules like other glandular cells; their absorptive power undoubtedly works in both directions. This assertion is not meant fully to support the old idea expressed by Ludwig, that the tubule was given its vast length to act as a corrective upon the lavish glomerulus, but we can well imagine that the epithelial cell is as free to act in one direction as in the other. Ludwig's idea was that the glomerulus, like a filter, passed out urinary constituents in the same degree of concentration as that in which they existed in the blood, and that subsequent alterations were the work of the tubule. It may be plainly said that his idea meets with little if any belief at the present day; yet one may insist that it is reasonable to suppose that the tubular epithelium does absorb from the lumen as well as from the blood.

Let us digress, at this point, to indicate some of the characters that the epithelium of the tuft and the epithelium of the tubules respectively possess. It has been shown that the somewhat flat epithelium of the tuft lies on the

[1] *Verhandl. der Deutschen path. Gesellschaft*, 1905, p. 73.

capillary directly, without the interposition of any lymph space. By its great superficial area it approximates to the endothelial cell of the capillary, and thus, in the glomerulus, where mechanical forces (*e. g.*, blood pressure) are prominent, the urinary water has to pass through only two flat cells, the inner capillary wall, and the outer flattened epithelial cell, which latter, by its shape and its absolute juxtaposition, can allow the fluid to pass as readily as can the capillary cell. But, on the other hand, it preserves enough of its epithelial quality to remember its function. It is a kind of frontier customs officer; it possesses complete power of allowing substances to pass, but, in addition, it possesses the power of selecting and turning back the undesirable elements. This is the specific power in which it surpasses its humbler endothelial brother. The tubule cell, on the other hand, works in an entirely different way. Between it and its capillary is a minute lymph space, and the lymph bathes it on one side and the urinary water in the lumen on the other. Here the layer of lymph exists to allow the cell to work, not in response to mechanical but to osmotic forces. The blood and the lymph make their exchanges, and the lymph and the cell make theirs; the lymph thus becomes a kind of middleman, and while breaking the continuity of mechanical forces, substitutes the medium by which osmosis can proceed. This being the case, it is readily understood that the osmotic process can go on as well from the urinary water to the lymph, by way of the cell, as from the lymph to the urinary water.

The Excretion of Water.—The most easily understood function of the kidney is the excretion of urinary water, mostly a glomerular but partly a tubular function; this varies in amount directly with the rapidity of flow through the renal vessels, which rapidity may or may not be connected with a rise or fall in blood pressure; a certain minimal blood pressure is necessary, but, if this be obtained, the effect of transient rises or falls in pressure is less apparent than the results got from an increased or decreased rapidity of flow. All these, however, fail if the blood is too concentrated (Henderson[1]).

Thus cardiovascular influences in general have their effect upon the excretion of urinary water, but the vasomotor influences exerted upon the kidney vessels themselves must be infinitely greater. Where these vasomotor stimuli arise and how they are conducted we do not know. Yet the results that depend upon them are at times remarkable. What is the mechanism of hysterical polyuria, and why may a cannula inserted in the ureter cause anuria? Why does moderate venous interference lessen instead of increase the amount of water? Again, what is to be made of the immense increase of urinary water which Rose Bradford found to follow the excision of large fractions of the kidney substance? Upon the answers to these questions we can only speculate, but, at least, they indicate how great is the elasticity of function in at least the matter of water excretion. While attention is directed to the importance of vasomotility, it must in addition be kept in mind that there is a cellular selective power in the epithelium and endothelium of the glomerular capillary, although we do not know whether the urinary water escapes through or between the cells or by both routes; whatever be the fact, the endothelium does possess a varying power of allowing fluid to pass, either by a shrinking of the cellular

[1] *American Journal of the Medical Sciences*, 1907, cxxxiv.

bulk and a consequent increase of the intercellular space, or by a distention of the vessel producing a flattening or thinning of the cells. It may be stated, however, as a probability that the excretion of urinary water is accomplished by a combination of several forces, acting together or separately, namely, the pressure and rapidity of the blood stream, the personal power of the capsular epithelium and the endothelial cells of the capillary, and obscure influences on either or both of these brought about by nervous stimuli; all of these, again, being to a large extent under the dominance of the local vasomotor nerves. The influences which act upon the output of urinary water are thus very far reaching, and are such as will react to many physiological, to say nothing of morbid changes; the difficulty of telling how far the kidney itself is at fault, or how far it is merely proving an adjuvant to some other system, is apparent. The kidney may act the last-named good part for the sake of some other organ, such as the heart, and it may do this so long and so continuously that it becomes a slave, and bears the brand of its master in a physical change which is indelible.

The Excretion of Solids.—The separation of the solid substances of the urine forms the next function of the kidney, and these substances fall at once into two groups, inherently useful materials (which are in excess, such as sugar in alimentary glycosuria, or which have served their purpose, as pigments), and substances that are inherently harmful. The latter class embraces many end products of metabolism which we are accustomed to consider as the normal constituents of urine, as well as accidental substances introduced from without and substances produced by pathogenic agents in the body. As has been indicated above, the power of excreting solids seems to be shared by the glomeruli with the tubular epithelium; in the glomeruli there is no doubt a certain degree of extrusion by mechanical force of substances in crystalloid or soluble form in the blood which are permitted by the glomerular epithelium to pass. It seems wrong to deny to the glomerular endothelium a certain ability of selection, because we admit it for capillary walls elsewhere in the body, and, if there be no selective power in the endothelium, that of the epithelium must be excreted through the barrier of the capillary wall. The epithelium appears to be able to take up the colloidal substances from the blood. The process here must be very complex—a combination of mechanical filtration, endothelial selection, more refined epithelial selection, and perhaps osmotic exchange as well. In the tubules, on the other hand (bearing in mind what has been said previously as to the isolation of the tubular cell by an infinitesimal layer of lymph), the process is reduced to a combination of selection and osmosis. Perhaps, after all, selection is but an expression of osmotic force. If we have any force other than osmosis, we must admit that it is exerted this time across the barrier of the lymph space and the basement membrane. Further, the renal epithelium has the power of synthesis, and forms complex substances that are not apparent as such in the blood or lymph, such as hippuric from benzoic acid, as well as the power of analysis, breaking down other substances, as kreatin to form kreatinin. These changes are due to the formation in the tubular cell of an enzyme, which has been called histozyme (Wells[1]), and it is a significant fact that it has an interchangeable action, changing benzoic acid and glycocol to hippuric

[1] *Journal of the American Medical Association*, January 25, 1902, xxxviii.

acid, and the contrary. The bearing of this quality upon the supposition that the renal epithelium is free to exert its powers toward absorption as well as toward excretion is obvious.

Lastly, has the kidney an internal secretion in the sense in which we speak of the secretion of the thyroid, the pituitary, or the adrenal? One is tempted to think so, although it must be admitted that we have no evidence that is undeniably certain;[1] unfortunately, extirpation of the kidneys is followed by death from symptoms which are explicable on other grounds than the absence of a specific secretion; but in nephrectomized animals death can be postponed for a short time, but not averted, by the administration of the juice of the fresh organ. The administration of raw kidneys in case of renal insufficiency has not yet been so successful as to enable us to deduce therefrom that a specific internal secretion exists.

In considering normal urinary excretion, it seems necessary, above all other things, to acknowledge the vast importance of the dependence of one part of the kidney mechanism on another, and the readiness with which one part takes up the work of another, remembering, at the same time, that there is a high degree of individuality in the renal cells themselves, so that the degree of functional activity or of implication by disease may vary greatly in different parts of the same organ.

THE PATHOLOGICAL PHYSIOLOGY OF THE KIDNEY.

The Relation between the Blood and Kidney Excretion.—While the kidney has a specific power of secretion or excretion which may be reserved for special occasions, or, on the other hand, which may be doing subsidiary work all the time, there is yet a very important, quasi-mechanical excretion going on constantly by the glomeruli. This was naturally one of the earliest facts to be observed. The glomerulus, a mere coil of capillary, was seen to have a large afferent and a small efferent vessel; the blood pressure at the source of the renal artery is high, that at the mouth of the renal vein low; it was thought that the excretion of urine by the glomeruli was the expression of the difference of force between these, plus the amount that was excreted in the secondary system by which the tubule is supplied. It will be remembered that the arteriæ interlobulares carry most of the blood entering the kidney directly to the glomeruli (although some of it goes to the vessels in the intertubular spaces), and that the efferent glomerular vessels are distributed to the intertubular tissue to supply the tubules after the blood has gone through the glomerulus. The kidney thus resembles a compound engine, in that most of, if not all, the blood goes to the high-pressure glomerulus, as the steam goes to the high-pressure cylinder, thence much of it goes to the low-pressure tubular capillaries, just as the steam, deprived of much of its expansive force, goes to the low-pressure cylinder; in all this the mechanical advantage is evident.

The result is that, ordinarily, the blood stream is inflicting a certain wear and tear on the glomerulus; the wear and tear depends upon the

[1] R. M. Pearce (*Archives of Internal Medicine*, 1908, ii, No. 1) presents a strong case against the existence of a specific internal secretion by the kidney in a paper which contains much useful material relating to urinary function.

amount of work that is being extorted from the mechanism, or, expressed differently, depends upon the persistence with which blood at high pressure is supplied to the glomeruli; the compound engine after a hard run is allowed rest, but the glomeruli have no such relief; in any middle-aged kidney, or a kidney that has experienced hard, continuous strain, there are the so-called hyaline glomeruli, which have still the form but none of the functions of glomeruli; as the body has no means of supplying new glomeruli, the blood force is no longer expended on the high-pressure glomeruli, but falls direct, to a great extent, upon the low-pressure secondary circulation, which was never built for such high-pressure work; it is likely, then, that degeneration goes on here all the more quickly, and the stress undoubtedly leads to a rapid fibrosis; it is not difficult to imagine that a degenerated glomerulus leads soon to a damaged or quite inefficient tubule, not only from the results of this stress, but because the inefficiency of the glomerulus brings it about that the tubular cells are no longer thoroughly washed by the free flow of urinary water.

Another factor, which seems no less important, is the *quality of blood* that is supplied to the entire capillary system; the blood brings deleterious substances which injure the structures in their passage, and the structures also have to take their nutrition from this source; the more deleterious substances there are the worse is the cell food, and, therefore, the poorer the work done by the cell; the cumulative quality of such a bad state of affairs is easily apparent. Thus it is brought to pass that the perfection of the selective power is lost, and substances that were once held back are allowed to pass through, and, on the other hand, substances whose appearance in the urine was dependent on kidney efficiency no longer appear there. In such circumstances the urinary water is excreted by skin and bowel; salts, such as chlorides, may escape by the intestine; nitrogen may, to a great extent, escape by the same way (von Noorden[1]), or even by the saliva in small amounts, and the well-being of the organism no longer depends on the broken-down kidney, but on the excellence of the adjuvant systems.

Tubular Functions and Disturbances.—The Functions of the Tubule and its Behavior when Irritated.—To the tubular epithelium we are in the habit of ascribing certain functions connected with the partial excretion of salts and other solids, as well as the synthesis of uric acid and the analysis of kreatin and other bodies; but these are doubtless but a small part of the work of so complex a structure, and our knowledge of the actual secretory power of the tubular cells is gathered from sadly uncertain modes of investigation; the convoluted tubule and the ascending loops of Henle excrete uric acid; but what is to be said for the tubular areas that as yet, like brain areas, are "silent?" What mean the modifications of epithelium in the various parts of the tubule? We can scarcely guess. One is tempted to indulge in the fancy that the tubule may some day be divided off as to function, in the same way as the alimentary tract is; that just as there is a specialized process in each part of the latter, there may be in the former; also, that the processes of absorption and re-absorption that go on repeatedly as the intestinal contents pass down may, perhaps in some less degree, be repeated in the tubule.

The convoluted parts of the tubules are those in which we mark most

[1] *Metabolism and Practical Medicine*, London, 1907, ii, 439.

constantly the changes wrought by toxins; in fact, the strictly medullary parts of the tubules are as yet of but little use to us, so far as the microscopic determination of pathological change is concerned. Analogy leads us to suppose that if these last were concerned only in conduction we would have a less specialized lining for them. Experiment with pigments in the hands of Heidenhain, Adams, and many others has proved useful in the determination of functions of different parts of the tubule; various pigments are put into the animal body, and when the animal is killed, after a shorter or longer period the position of the pigment granules in the kidney cell is determined. The conclusions drawn therefrom are open to the objection that the position of pigment in the cell is not necessarily an indication of its route, but, if sufficient of such experiments be carried out, it it is safe to assume that the distance (in the cell from the lining membrane) that the pigment has progressed in animals killed at various times after injection indicates whether the pigment is taken up from the blood or from the urine. It must be admitted, of course, that experimental animals are not exactly normal, and the very "give and take" of one part of the tubule and another may perchance lead substances to be excreted in a way differing from that in the normal kidney.

The tubular cell is prompt to suffer from the effect of even transitory toxicity of the blood and lymph; with reference to the lymph, indeed, we will do well to remember that the lymph which bathes the cells intercellularly probably acts precisely as does the blood with reference to excretion, save that, there being no high pressure in its current, it exchanges its constituents with the urine merely by osmotic variations of the two fluids. To toxic lymph and blood the cell quickly reacts, entering the state of cloudy swelling; this is the peculiar "ground-glass" appearance that the individual cell takes when it is damaged, and the kidney of almost every infective or toxic case shows it so distinctly that it can be determined by the naked eye. It probably is often undergone by cells in the course of life, and from it the cell can recover entirely. Careful study of the cell with cloudy swelling indicates that there is a disturbance of the osmotic relations, by which the bulk of the cell becomes much greater; the Altmann granules, instead of being arranged in definite rows, appear to be dislocated from this arrangement and are seen in apparent disorder. The cell in this state is undoubtedly less efficient, and, as was pointed out earlier in this chapter, there is at once a less perfect excretion by the cell, and its own catabolism is increased. So the vicious process continues until the individual cell has gone on to the stages of granular, fatty, or hyaline degeneration, as the case may be, all of which are supposedly more extreme than cloudy swelling; it may well be imagined that the results upon excretion are to lessen its efficient performance. Such a condition may become the beginning of a permanent insufficiency, and the kidney tubule may not be able to regain its state of perfect health.

When considering the damage wrought upon the kidney by toxins, it is essential, however, never to lose sight of the fact that there are two widely different classes of tissue involved, the parenchyma and the connective tissue. These differ widely in the extent of their reaction to irritation. The writer is in the habit of using a fanciful illustration for this: the parenchymatous cell represents the "professional man" in the community, specially trained, not to be replaced but by one of his own class, impressionable by even slight external stimuli, not prone to be physically hardy or overgiven

to reproduction. The supportive cell, on the other hand, is its "laboring-class" brother, not trained in any high, special task, whose supportive work can be replaced by any kind of tissue, even scar tissue, not readily impressionable, even by powerful, external stimuli, physically strong, and ready in reproduction. These two cells lie side by side in the kidney, exposed to the same toxic influences, but reacting to them each in its own way. A toxin strong enough seriously to damage the high-class cell is only strong enough to irritate the low-class cell to reproduction. When the high-class cell is killed by toxin, it leaves no one of its kind in its stead, and its place is occupied, but its function is not performed, by the progeny of its laboring-class brother. If some such plan be kept in mind, one is prepared to collate the effects of toxin upon each kind of tissue, and so to form a right idea of the *total* result in the organ. When the condition of imperfect tubular excretion, referred to above, is prolonged, many cells die and are desquamated, and the toxins which sufficed to damage and even kill the cells are sufficiently potent to irritate the supportive structures to overgrowth; thus, hand in hand, the two processes go on until there is proliferated connective tissue where once was a tubule, and this is the process of fibrosis. The work of every destroyed tubule must be thrown on its surviving fellows, and if the kidney continue to perform its work apparently perfectly, it is done, nevertheless, at a price; the price is stress, which will have to be paid for by shortened life of the other tubules.

The Effects of Toxins.—What are the effective toxins? They are the toxins, so-called, of the infective diseases, products of cell catabolism throughout the body, hæmoglobin (Levy[1]), many irritant exogenous poisons (of plant and animal origin), and perhaps many chemical products which we are accustomed to consider as the normal output of the kidney. This apparently brief narration includes a vast number of substances. The products of pathogenic bacteria are well known as having an irritant action on the kidney, but there are doubtless products of bacteria not known to be pathogenic, which also irritate; the great numbers of bacteria in the alimentary canal are constantly producing substances with which the kidney has in part to reckon; and in constipation this responsibility is doubtless increased. Every cell that breaks down in the body has to be disposed of, and in cases of extensive damage, as burns, suppurations, and necroses, the kidney has to bear its share of the excretion. With reference to exogenous substances, we have but to look at the belief that one food is better than another, that the red meats are harder on the kidneys than white meats, and a hundred other facts or fancies that make up our ideas upon diet; be they truths or errors, we have but to observe these to see that the practitioners of medicine at least have given a large place to the responsibility of the end products of ingesta with regard to the kidneys.

The Effects of Age.—The changes produced by age may be considered physiological, and doubtless are, but physiological in the sense of being processes which are always occurring, which we consider hurtful, but which cannot be obviated. Every "old kidney" shows certain changes which appear to be of the nature of replacement fibrosis such as we have previously described; they appear to co-exist with changes in the arteries, and in the very old make up a well-defined entity. What, then, are the

[1] *Deutsch. Arch. f. klin. Med.*, 1904, lxxxi.

causative factors here? If we knew the cause of arteriosclerosis the question would probably be answered: work, catabolism, stress, the hundred slight disturbances of all the tissues (whose catabolic effects must be disposed of), the fact that nothing lasts forever, the sudden jars, metabolic and chemical, of a blood supply no longer perfectly cushioned by elastic arteries—these, and as many more, perhaps, go to make up the factors which cause the changes of age. The constant breaking down of cells is a strain on the kidney, the greater by so much as the kidney is older; but it must be said, on the contrary side, that the very fact that the body is smaller and the cells fewer is of advantage to the kidney, because the output of such cells is less than in the body of full manhood; there is thus a kindly compensation, even in old age, which tends relatively to lighten the renal labors.

Nevertheless, it often appears that the "old" kidney is a very efficient one; and this compensation is a virtue not to be ascribed more to the kidney than to the circulation. As the arteries become old and inelastic, the heart can no longer depend upon them for the necessary contractions which tend to raise blood-pressure in localized areas, and must perforce work harder and adopt a higher general standard of minimum blood pressure, which is accomplished by hypertrophy. From the time at which this raising of the minimum blood pressure commences, the tissues, even when most at rest, are yet exposed to a strain greater than that to which they have been accustomed; with the increasing inelasticity the minimal blood pressure continues to rise. The kidney shares to the full degree in bearing this strain, and the constant stimulation—mechanical if no other—leads to productive processes in the supportive structures.

Parenchymatous Change in General.—Albuminuria and Casts.—As the kidney tubule is the unit of the kidney, and, so far as we can see, every tubule is built exactly like every other one, the parenchymatous derangements of the kidney can be narrowed down to the sum of the derangements of the single tubules, derangements that vary from cloudy swelling to complete disappearance and replacement. Slight changes often pass unnoticed, so far as any urinary sign is concerned, and, on the other hand, there are slight urinary changes, such as transitory albuminuria, with which we have not yet learned to coördinate the corresponding alteration in the kidney. Without entering into the question of albuminuria, it may be said that these transitory albuminurias must have a meaning; albumin has its place, and its place is not in the urine, so that "physiological," as a term applied to albuminuria, ought to mean not a normal process, but a process so little abnormal that experience has led us to know that certain cases of it do not habitually lead to any more serious disturbance. Albuminuria can depend, too, upon causes which are not situated in the kidney itself; anything that prevents the exit of venous blood from the kidney may cause albuminuria, experimental temporary blocking of the renal artery may cause it, the upright position in some persons seems to cause it, or, to put it in another way, the recumbent position causes its cessation, and the distribution of increased pressure in pregnancy has been held to explain the presence of albuminuria. Under these circumstances, all or most of the albumin is excreted by the glomeruli. But in its occurrence, when there is disease of the kidney, the site of its output is uncertain, and may be tubular as well as glomerular.

Here it is in place, also, to make reference to casts. The blood cast is an

evidence of rupture of a capillary or other vessel in the glandular part of the kidney. The source of the epithelial cast is equally obvious, although it is formed sometimes of the original tubular lining and sometimes of epithelium that has been newly generated by the tubular cells; the histological nature of the cells concerned gives no accurate information as to the site of its formation, and in all cases it must be remembered that the cast, when seen in the tissues, may be on its way out, and is not necessarily at the site of its formation; epithelial casts can be formed, too, by agglomeration of cells, so that the juxtaposition of its individual members does not always mean that they occupied that place in life, although it generally does so. Some hyaline casts are also of epithelial origin, although it is not possible to say whether the hyalinization occurred in life or after they were detached. Whenever they can be recognized as epithelial, casts mean that the kidney substance is, to this extent, destroyed. It is true that, normally, kidney cells are constantly paying their debt to nature by dying, and as such are being shed off, more or less altered. The appearance of single cells in the urine thus means nothing, but with aggregations of them it is different; if one may use a simile of a homely kind, the deaths of many men here and there in a community do no more than remind us of our mortality; but when a dozen members of one family circle die, we proceed anxiously to inquire into the cause. This is the state of affairs in the renal community when a cast appears; there is a local upsetting of normal conditions where it originated. The statement has just been made that some hyaline casts are of epithelial origin; perhaps the majority are, but the subject has been the battleground of much controversy. It seems reasonable to suppose that hyaline casts can originate in three ways, from the epithelium itself, shed and altered, from coagulation of transuded plasma, and as an excretion of the tubular epithelium, or, better, as a separation of part of the tubular epithelium. These will be dealt with in their order.

Langhans[1] demonstrated the colloid alteration that epithelial cells undergo, by which they become glassy and transparent. Ribbert has long championed the second theory of formation; he considers that casts are formed of albuminous transudate hyalinized by the acid reaction of the kidney. His experiments certainly seem to bear out the contention, but Saundby[2] concludes from their rarity in functional albuminuria that this is not a common source. Some hyaline casts give the reactions of fibrin and some do not. The supporters of the third theory contend that hyaline casts may be formed by the shedding off of material which is either the cell substance itself, that has imbibed water and has swollen up, or is an excreted product of the cell. The material referred to can be seen in tubules of a kidney which is the seat of moderate nephritis, and consists of globules or masses of varying size, which look like irregular droplets, which appear to be able to fuse together, and which at times appear to be only the spaces between the meshes of the detritus that is seen in the lumina. Ribbert contends that these are normal. Where such are present, the epithelium is often found low and, as it were, lopped off; when the epithelium is not truncated, it may be that the material has descended from a higher part of the tubule. It will be at once evident that a growing vital part of the cell is yet left, and

[1] *Virchow's Archiv*, 1879, lxxvi.
[2] *Lectures on Renal and Urinary Diseases*, second edition, p. 41.

this may be the reason why a kidney can produce vast numbers of such casts through a series of years, without suffering greatly in the process. Oertel[1] and Rovida long ago pointed out these "plasma rings," and discussed their probable relationship to hyaline casts. Bartels considered that the hyaline cast is generally formed from an excretion of the cells, while admitting the possibility of its formation from the coagulation of albumin. Councilman,[2] who has carefully studied the kidney, will not venture an opinion upon the nature of these structures, but, on the other hand, admits the likelihood that fibrin can form casts. There is good reason to suppose that hyaline casts arise in all three ways, as Saundby stated some years ago. All of them indicate a pathological state of the secreting structures, and a hyaline cast, therefore, viewed in its most innocent light, is an indicator of disease.

Even when the cells are shed off in numbers as casts, it is well to recall that kidney epithelium can be regenerated to a moderate extent over denuded areas.

Changes in the Glomeruli.—The changes which are found in the glomerulus in different forms of disease are manifold, but it is hard to refrain from grouping them into those which signify acute disease and those which signify chronic change, although the boundary between the two is difficult to place. It may be of advantage to point out these alterations, leaving their exact application to the articles which deal with the diseases themselves.

The Capsular Space.—Exudation of albuminous fluid, and subsequent fibrin formation can occur, and this may either be absorbed, swept away, or may remain and become organized, so that partial or complete adhesion between the walls of the capsular space may occur, and, further, the glomerulus itself may become secondarily vascularized by new-formed vessels which run from the peripheral wall. Hemorrhage may occur into the capsular space. The lining epithelium may be so damaged as to become swollen, granular, and may be desquamated in a moderately undamaged or in a necrotic state, or in cases of less extensive damage it may actively proliferate. Degenerated cells pushed up from the tubules may appear in the capsular space, as was shown by Welch in the kidneys of cantharidin poisoning. In all this one may see, as has been suggested, the parallel that exists between the capsular cavity and the serous cavities, such as the pleura or the peritoneum (Cornil[3]). It is not mere coincidence, but shows that the reaction to inflammatory, regressive, and progressive changes is everywhere in obedience to law.

The Capillaries of the Glomerulus.—In the capillary branches may be found bacterial, fibrinous, or hyaline thrombi; leukocytes emigrating through the walls have been seen by Councilman, although the occurrence of this phenomenon had for long been denied; cells, evidently the proliferated endothelium, are seen, sometimes yet adherent, at other times desquamated and degenerated. An increase of the cells between the capillaries is at times to be seen, which cells may prove to be mainly leukocytes; this is, naturally, the result of the emigration spoken of above, and this infiltration is not to be found elsewhere in the kidney, indicating clearly the existence of irritants

[1] *Deutsch. Arch. f. klin. Med.*, 1871, viii.
[2] *Medical and Surgical Reports of the Boston City Hospital*, 1897.
[3] "La Glomerulite," *La Presse Médicale*, 1900, i, 177.

whose "first choice" is the glomerulus. The entire glomerulus rarely may be converted into a granular, necrotic mass, in which no individual features can be distinguished (Councilman[1]). Amyloid change of the capillary is familiarly known, and most common of all is the hyaline change, which affects the vascular wall; whether it occurs on its outer surface or its inner surface is uncertain, but the change begins in the distal parts of the loops and progresses until the lumen is partly or wholly occluded, and the entire tuft is replaced by a hyaline mass, with an occasional narrowed blood space, whose scattered nuclei still may be distinguished. Finally, the intercapillary connective tissue may be proliferated and the new-formed tissue finally shrink, pulling in the surface of the tuft by its contracting bands, just as happens in a "hepar lobatum" or a "granular" kidney; this constitutes the lobulation that is at times so characteristic a mark of the damaged glomerulus.

The effect of the above-mentioned chronic changes on the size and appearance of the glomerulus can be well imagined. Side by side with small, hyaline, useless glomeruli will be found others of great size, which by compensatory hypertrophy are capable of doing their own work and more; the excess of urine in cases of interstitial nephritis is probably partly due to the high efficiency of these hypertrophied glomeruli, at least so far as the excretion of water is concerned.

Changes in the Tubule.—The alterations produced in the tubule are more simple than those in the glomerulus; we have here to consider only the changes that the individual cell may undergo. These are the various degenerations, cloudy, granular, hyaline, fatty, and "dropsical," vesicular or vacuolar; as a result of degeneration the cell may be desquamated individually, or with others as a cast; it may be thrown off and become cemented to others while in the tubule, again forming a cast, or it may become necrotic and disappear as quickly scattered debris. It may present variations of size and of shape, which variations in turn affect the capacity of the lumen of the tubule. Into the tubule may be thrown blood or the precursors of fibrin, with subsequent formation thereof. All degrees of variation of the size of the lumen are found from the narrow lumen of cloudy swelling to the cyst. All changes in the epithelial cell are but temporary, and must be considered as acute, in the sense that a cell will not live long in a damaged condition. When the cell dies, its neighbors may be able to generate a new cell to take its place, which, in its turn, may undergo similar changes; if no such substitute is formed, the tubule, as such, ceases to exist, or remains only as a space in the connective tissue; if its glomerulus also be destroyed, even the space ceases to exist, and solid fibrous tissue finally replaces it.

The deleterious agents which affect the tubular epithelium may be in the blood or in the urine, and in either case the chances are that the glomerulus will have been first exposed to their action.

Changes in the Interstitial Tissue.—Space need not be occupied in describing the changes that the connective-tissue stroma undergoes, for these are the same as are undergone elsewhere by supportive tissues; it may be the seat of a migration of leukocytes, or an active or a passive œdema, of a liquefying or a coagulation necrosis, or of any one of the many degrees of proliferation of its own elements with subsequent fibrosis. These changes do not always march shoulder to shoulder with changes in the connective

[1] *Medical and Surgical Reports of the Boston City Hospital*, 1897.

tissue of the glomerulus, because the latter have peculiar opportunities for exposure to irritants. The capsule of the kidney is practically one with the stroma of the organ, and need not be separately considered. Variations in the size of the organ are assisted not only by the changes in the total mass of the interstitial tissue, but also by variations in the size of individual tubules and glomeruli, to say nothing of the variation in bulk of the blood-vessels and their contents.

NEPHRITIS.

Let us be thoroughly theoretical for a moment, and say that a nomenclature of nephritis (of every kind) cannot be perfect until we describe every kidney in terms of the changes that exist in (1) the glomerulus, (2) the tubule, and (3) the interstitial tissue. Even now we are assuming that the tubule is a unit, whereas a fuller knowledge of its different parts may prove it to be divisible; the accurate description of a particular kidney ought to be denoted as follows: glomerulus, change of x degree, tubule, change of y degree, interstitial tissue, change of z degree; another kidney would show glomerulus, change of r degree, tubule, change of s degree, interstitial tissue, change of t degree. We have indicated a dozen variations, temporary or permanent, in the glomerulus, any one of which may be accompanied by one or more of the variations to which the tubule is liable; combinations thus made by mathematical process are, to say the least, numerous; when we go farther, and find that every such combination may be again combined with anyone of the variations in the interstitial tissue, the possibilities are legion. Such a nomenclature, alas, is quite impracticable; yet every classification of nephritic conditions which has been promulgated is an attempt to sort out this almost infinite series, and the classification that disposes of most is the best, but is equally certain to be the largest and most unwieldy. Most of us are content to use a working method of classification and nomenclature, by which we name the lesion by the feature which happens to predominate. Yet two kidneys may present the same predominant feature, while the other characters may differ widely, and even the same predominant feature may sometimes have been attained by widely different processes. Having pointed out the inexactness of the "nomenclature of the predominant feature," we are inconsistent enough to fall back upon it.

It is with an apology that one ventures upon the oft-trodden ground of Bright's disease, especially because the subject will be dealt with elsewhere. Bright's disease comprises acute and chronic parenchymatous nephritis, chronic interstitial nephritis, and that form of acute interstitial nephritis characterized by an infiltration of fibroblasts, but not by leukocytes (scarlatinal nephritis), all of which are toxic, not infective, nephritides; that is, the bacteria are not pathogenically present in the kidney itself, as occurs in calculous, tuberculous, or other true infective acute nephritides. It is timely here to point out that those who make distinctions between chronic parenchymatous and chronic interstitial nephritis do so with the understanding that neither one ever exists alone; interstitial change never exists without an accompanying parenchymatous change, undoubtedly brought about in successive generations of tubular cells by the same agent, and parenchymatous change cannot exist long without interstitial alteration following or accompanying it. Acute parenchymatous nephritis may be produced in

a very short time, a matter of hours, perhaps minutes, and obviously cannot be accompanied by an instantly produced fibrosis, for the nature of the latter process is that it can only be slowly produced. An observable acute parenchymatous nephritis can, however, occur in any kidney, fibrosed though it be, provided that enough tubules be left to enable us to see the change. We may go even farther than this, and say that the process we call chronic interstitial nephritis, strictly speaking, is no more than a series of slight consecutive acute attacks, each of which leaves a few more fibroblasts behind, and that in the intervals, although the results of previous acute attacks remain, yet the disease is at an absolute standstill. The "ups and downs" of a nephritic are familiar to us; the exacerbations referred to constitute the "downs."

There are many terms constantly used to indicate the various types of kidney found in nephritics, and one hears of small white kidneys, large red kidneys, small red kidneys, large white kidneys, and yellow kidneys, until one may be forgiven if he becomes confused; we do well to remember the extreme uncertainty of predicting the kind of kidney from the clinical symptoms and signs, and the habit of referring certain clinical signs to a "large white kidney" or some other such kind is to be discouraged.

The Varieties of Nephritic Kidney.—In terms of our present-day nomenclature, however, there are some observations to be made. We have indicated above that the two main forms of chronic kidney damage go hand in hand; there is in reality a wide range of lesions, at the extremes of which stand, at one end, the kidney whose most prominent characters are parenchymatous; at the other end, the kidney whose most outstanding character is interstitial change. Between lies every possible degree of combination. When we find a kidney which combines the characters of both to such a degree that neither stands out, we make a compromise, and call it a mixed nephritis.

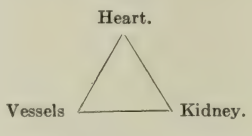
The changes that especially mark parenchymatous change are that the kidney is big, plump, firm, yet resilient, often "hog-backed," and it has a wide cortex, often swollen. Those that indicate the kidney of the interstitial type are that it is small, hard, nodular, with a large fatty pelvis and a narrow irregular cortex. The former kidney is generally red, the latter pale, and these two are the types called "large red" and "small white." Further color modifications of these may exist according to the more or less accidental amount of blood in the organ at the time of death, although it would not be correct to say that the presence or absence of excess of blood is a fortuitous circumstance. Anæmia of the body causes pallor of the kidneys as of other organs, and hyperæmia, active or passive, will give a dark red color; fatty change in the epithelium may be so extreme as to give a yellowish or dirty white color to the cortical structures,[1] and a combination of this with hyperæmia is one of the sources of the so-called "mottled" kidney.

Is there any relationship of these large and small kidneys one to the other? It has been known since the days of Bright that some large kidneys of the parenchymatous type progressed to become small ones of the interstitial variety. This is probably always so, provided the patient lives sufficiently long, but many succumb while the kidneys are yet large. There are, how-

[1] Kidneys of this color may fail to give the chemical reactions of fat.

ever, small granular kidneys that have never been larger than normal, that have, on the contrary, undergone a slow replacement fibrosis—the so-called primary renal cirrhosis or granular atrophy. The end result of this process does not markedly differ from the end result of interstitial nephritis, but it is presumably a process of quite different etiology.

These interstitial changes in the kidney are intimately connected in many cases with hypertrophy of the heart, especially of the left ventricle, and with arteriosclerosis; we find that many people die with certain lesions of these three systems in whom one cannot lay the blame on one system rather than on another. Does the hypertrophied heart lay so much stress upon the vessels and the kidney as to damage them, or does the vascular change precede the others, or is the renal lesion the primary one, or is some widespread toxin responsible for all three at the same time? Speculation upon these questions is as yet unending, and so much has been brought forward in support of a positive answer to each one that no firm basis yet exists on which to make a decision. For purposes of demonstration to students, the writer is in the habit of indicating the combination diagrammatically by an equilateral triangle; at one angle is *heart*, at another *vessels*, and at the third *kidney*, thus:



Then having pointed out the intimate physiological relationship existing among the three, one may rotate the triangle, and it matters little which angle comes uppermost, as the three constitute a "triple alliance," which may fairly be said to represent an entity of disease.

Changes in the stroma of the kidney, however extensive, are not of themselves reflected in the urine, but the accompanying parenchymatous alterations are, and it is the glomerular and tubular defects which give the urine its pathological characters. But we have, by long observation, been able to see that the parenchymatous and interstitial changes go together in such definite proportions that we are able to prognosticate the latter from the former. In a general way, a granular kidney is associated oftenest with much urine of low specific gravity and little albumin, whereas the large parenchymatous kidney is often associated with a more moderate amount of urine, with much greater albumin loss, and more frequent casts. As for frequency of casts, we have to remember that their numbers must never be considered apart from the quantity of the urine, and that the degree of disease being equal, the kidney with most tubules will shed most casts.

The uncertainty of prediction of the extent of disease from the observation of the kind and number of the casts is very great. Max Brödel, of the Johns Hopkins Hospital, has compiled some interesting figures as to the number of tubules and glomeruli in the normal kidney.[1] He has estimated that there are approximately 4,000,000 tubules and glomeruli in the two kidneys, aggregating about 75 miles in length; when we consider that

[1] An account of this will appear in full in a forthcoming work on the *Surgery of the Kidney*, by Howard A. Kelly.

a urinary examination takes cognizance of the production of casts or the shedding of epithelium from but an infinitesimally small part of this area, and that all forms of change resolve themselves into three or four different kinds of casts, it seems reasonable to make mental reservations with any stated diagnosis which is based upon the number and the kind of casts present.

THE KIDNEYS AND FOOD AND DRINK.

The statement frequently made, "that more men die from overeating than from overdrinking," if true, refers no less to the kidneys than to the liver. Most articles of diet, in analysis, prove to contain one or other of a long list of substances which are not easily excreted; they impose extra work upon the healthy kidney, and they are able to damage the unhealthy kidney. To restrict a healthy man's food because of a possible danger to his kidneys is not necessarily rational, even if it were possible; but we should adopt every means we can to spare labor to the already diseased kidney, and to the healthy kidney in times of stress, such as occur during the course of fever, of infections and of intoxications. In these last the kidney may be so near the point of breaking down, that injudicious diet may supply the necessary additional irritation to cause the break-down.

We have a preconceived idea that bland substances with a high proportion of water are kindly toward the kidney, while substances or fluids that are highly diuretic are considered to entail increased work upon the organ, and many condiments are thought to be actually injurious. These views appear in the main to be correct. In one sense, water is the best diuretic, and it is possible to wash the tissues as it is possible to wash the face, the ingestion of increased water and the consequent increased output of urine advancing the metabolic overturn in the whole body. But circumstances alter cases. We must agree with von Noorden and his school when they declare that there are times when the kidneys refuse to be washed; these observers have held with much reason that a kidney totally insufficient, that is, the kidney of anuria, is as unable to execrete water as anything else. Von Noorden even goes so far as to hold that to such a kidney water is as irritant as urea. Whether this be accurate or not, the kidney as persistently refuses to excrete the one as the other; they therefore advise restriction of fluids, which is rational enough in this, that when the blood pressure tends to be high and œdema is occurring, it is useless, or worse, to add to both. As soon, however, as the kidney begins to express its readiness by a resumption of its water excreting function, the time has come when it will submit to washing, and they admit the desirability of so doing.

When the kidney incompetence is evident, as in anuric or oliguric conditions, the withholding of food may be necessary; but in cases in which the physician is required to exercise supervision lest the kidney be damaged by an infective disease, when his work is really preventive rather than curative, what form of diet may he adopt? We must supply the body with food whose products are easily excreted, and we must avoid the use of drugs that are difficult of excretion. It is generally admitted that urea, creatin, hippuric acid, and phosphates are hard upon the kidneys. Urea is the result of ingestion of albuminous food; creatin exists largely in meat extracts and broths; meats and eggs are essentially protein, milk is moderately so, cream much

less so than milk, starchy foods scarcely at all. Cereals, fresh vegetables, and boiled fruits are also innocent in this regard. Green vegetables, fruits containing kernels, and cranberries contain relatively large amounts of benzoic acid, which is synthetized to hippuric acid, which also is difficult of excretion; apples, pears, grapes and raspberries contain little of it. Phosphates are largely present in meats, eggs, and milk; but von Noorden and others point out that the use of calcium carbonate with milk causes the excretion of much of the phosphoric acid by way of the alimentary tract, so that in this way the work entailed by a milk diet can be largely reduced; uric acid and the alloxuric bases come especially from meat glands, such as thymus, liver, and kidneys, and are moderately toxic to the kidneys; meats of all kinds contain extractives, and the so-called dark meats to a greater extent than the light meats. Adler,[1] in a late review of the subject, concludes that the prevalent idea that the subject of renal disease ought to eat light rather than dark meats is correct, and that these meats boiled contain the harmful factors less than when roasted.

Of all the articles of every-day diet, what is left to us to use that will not entail work upon the kidney? Judged by analysis, and supported by empirical knowledge, milk is a more suitable food than any other thing; but this is not meant to be a declaration in favor of "milk diet" as a routine treatment of renal insufficiency, because evil has been wrought by a slavish adherence to milk diet, as if it were a rule. Condiments which are generally supposed to impose work upon the kidneys are pepper, curry, mustard, garlic, and nutmeg; and with reference to drugs, one does well to remember the effects of cantharides, copaiba, turpentine, salicylates, carbolic acid, resorcin, lead, copper, silver, mercury, and boric acid, and even iodoform and tar preparations.

These statements are not made with any view to declaring a treatment for renal incompetence, or of forestalling the articles dealing with the renal diseases, but merely as a kind of working basis that one may keep in mind as an assistance in determining a diet in any case of illness in which the kidneys are specially liable to attack (as in scarlet fever), or in any case in which a damaged kidney leads one to be cautious lest the disease be aggravated.

[1] *Berl. klin. Woch.*, 1908, xlv, No. 8.

CHAPTER II.

MALFORMATIONS OF THE KIDNEY—CIRCULATORY DISTURBANCES OF THE KIDNEY.

By JOHN McCRAE, M.B. (Tor.), M.R.C.P. (Lond.).

MALFORMATIONS OF THE KIDNEY.

The malformations of the kidney are of very slight clinical importance, especially to the physician; most of them, in fact, are but curiosities, which lie undiscovered unless disclosed at autopsy.

Absence.—Total absence of kidney tissue is generally combined with abnormalities of the sexual organs, and is not consistent with viability. There are in existence case reports professing the contrary, but they are not credible.

Absence of one kidney, however, is fairly common, the writer having seen eight cases at autopsy. It is said, however, that in many so-called cases of absence of the kidney careful examination of the connective tissues of the region reveals that kidney substance may exist. No such microscopic examination was made in the eight cases to which reference is made. Once it was associated with a bicornuate, and once with a unicornuate uterus, and in many cases some anomaly of the sexual organs exists in association with it. The adrenal generally exists independent of the absence of the kidney, and sometimes a blind ureter opens to the bladder. The importance of this last fact is that the cystoscopic finding of a ureteral orifice is not perfect evidence of the existence of a kidney. The blocking of a ureter by any cause becomes much more serious in a case of unilateral kidney than in a normal case, but this has a surgical rather than a medical bearing. Cases of unilateral kidney are generally provided with a normal or almost normal amount of kidney tissue, thanks to the hypertrophy or hyperplasia of the existing organ. The chief practical point in connection with unilateral absence of the kidney is that it gives a rational basis for the surgical rule that before a nephrectomy is performed the presence of the other kidney must be demonstrated. The writer was present on one occasion in which the surgeon's care in this respect prevented him from removing the only kidney.

Anomalies of Shape and Position.—Persistence of the fetal lobulation of the kidney is at times observed, but has no clinical importance, nor have those departures from the conventional shape of the organ which are often seen. Sometimes the kidney assumes a shape which bears no resemblance to the normal organ, but this is not generally associated with any reduction in quantity of the kidney tissue, and makes not the slightest difference to the possessor. Fusion of the kidneys is chiefly of anatomical interest, the most familiar form being the well-known horseshoe kidney, in which the lower poles of the two organs are joined by a bridge of kidney tissue.

Displacements.—The kidney may be fixed in almost any abnormal position on the posterior wall of the abdominal cavity, most frequently at the edge of the pelvis; an organ so situated may be at times palpated, and may cause confusion in diagnosis, but no rule can be laid down for the avoidance of such a mistake.

Mobility.—This is not the place to discuss the important subject of movable kidney, but it may be pointed out that gradations of mobility exist, from the kidney which is all but fixed to that which can be pushed into any corner of the abdominal cavity. These latter, although their dislocation is largely an acquired character, have probably a congenital laxity of fixation from the first. Anomalies of shape and site are not infrequently combined with undue mobility, when the latter is of congenital origin.

Congenital Cystic Kidney.—The condition known as cystic kidney is at times congenital. Both kidneys, more rarely one, are composed of a number of thin-walled sacs, of varying size, containing usually clear, yellowish fluid; these cavities are sometimes lined with epithelium-like cells and are closed. The walls are fibrous, and may contain islands of renal parenchyma. Such kidneys may be found in the fœtus, sometimes so large as to impede labor, or in the infant, or finally, in the adult past middle age. While these are found at an age past middle life, it by no means follows that they have developed in adult life; it is generally conceded that they have a congenital basis. The statement that they are rarely found before fifty years of age may be due to the fact that the rest of the kidney substance is adequate until the time of the discovery, that the renal competence of earlier years is sufficient to tide over the possessor of a cystic kidney until that age. In the light of our knowledge of cysts resulting from nephritis, it is not easy to imagine any other than a congenital beginning for those completely cystic kidneys that are observed in advanced life; it must be admitted that the sacs may have greatly increased in size as time progressed.

The generally accepted view of the causation of congenital cysts of the kidney is that failure occurs in the accurate junction of the masses of nephrogenic tissue (later called the renal vesicles, which ultimately form the tubules proper), with the outgrowths from the Wolffian duct which form the pelvis of the kidney.

A strange feature of this anomaly is that it has been found in several members of the same family, and mother and daughter have been observed similarly afflicted. It has been found, also, associated with cysts of the liver, and in a case from our own laboratory with cysts of the liver and pancreas. Professor Adami, discussing the latter case, thinks that the so-called cystic diathesis is rather a disposition to failure to overcome moderate obstruction of the ducts than a real liability to the formation of cysts. The cystic part of the kidney takes little or no part in urinary secretion, although it is conceivable that tubules might still remain in the walls of the cystic sacs; for all practical purposes the cystic part of the kidney has no influence for good or evil in the urine. Symptoms have been sometimes credited to a cystic kidney that really belonged to the other non-cystic organ.

The special features of the condition in adult life are: (*a*) Bilateral renal tumors, the location of which is usually readily recognized; (*b*) the occurrence of hæmaturia, which may be present at long intervals over a period of years; and (*c*) the usual urinary findings of chronic interstitial nephritis with the common changes in the vascular system, arteriosclerosis and

cardiac hypertrophy. Osler has noted the occurrence of marked pigmentation of the skin in some cases. The termination is usually from uræmia or cardiac failure, rarely from complications which follow the rupture of a cyst. The treatment is that of chronic nephritis, except in the rare cases in which the condition is unilateral, when removal of the affected kidney is possible.

CIRCULATORY DISTURBANCES IN THE KIDNEY.

Anæmia.—Anæmia or ischæmia of the kidney may result as part of a general anæmia, such as occurs in cancer, tuberculosis, or pernicious anæmia, or may be caused by local agents of an organic kind which prevent ingress of blood to the kidney, or it may result from spasmodic contraction of the arterial wall.

When there is a general anæmia of all the tissues, the effect upon the kidney is that it undergoes a slow process of degeneration, produced by imperfect nutrition of the cells or imperfect removal of the waste products; this, however, is of little practical moment, as it is overshadowed by the effects of more important changes in other organs. The ultimate result may be an advanced stage of fatty degeneration of the parenchyma. Local anæmia of the kidney may be produced by narrowing of the lumen from disease of the arterial wall, or by the pressure of tumors or adhesions upon the artery; if severe and long continued, the amount of the urine will be lessened, even to the extent of anuria; if the pressure be slight or temporary, its effects will scarcely be reflected in any urinary change. There are some cases of anuria, the so-called hysterical ones, which are presumably due to anæmia, produced by spasm of the arteries, and here also must be placed, for the present, those cases in which anuria results in one kidney from injury or irritation of the other kidney or of its ureter. We shall not endeavor to recite the anatomical appearances found as a result of anæmia pure and simple, because we never see them except in experimental animals; nor the clinical signs, because there are none (save lessening of the quantity of urine), which can be safely asserted to be the result of ischæmia alone.

Hyperæmia.—The kidneys frequently become hyperæmic, yet this condition does not form a striking entity, because the cases in which it happens are generally of such a kind that organs elsewhere in the body are more deeply concerned. Active hyperæmia, such as occurs in inflammatory diseases, does not concern us here; passive hyperæmia, however, arises in two ways, either as part of a general venous stasis, or as the result of alterations of the freedom of circulation which are local to the kidney.

Considering venous stasis in general, it may be pointed out that the venous outflow from the kidney will be lessened when the blood cannot pass freely to the heart, because of direct obstruction in its path, or when the current is slowed because the arterial force (primarily the heart) is weak. In conditions of cardiac incompetency both of these factors may be at work, and the question which one is most effective is not of consequence. When the heart is incompetent and the arterial flow weak, the result is cortical and especially glomerular congestion, with excretion of albumin into the capsules. This much follows experimentation; the results of local venous stasis are felt first, on the contrary, in the medulla. If the two work together, the entire kidney is engorged, there is excretion of albumin, and the epithelium

of the tubules suffers by reason of imperfect oxygenation, imperfect nutrition, inability to get rid of its excretions by way of the blood, or a combination of these. The result is its degeneration. Such a kidney, seen macroscopically, is large, firm, and dark red; its capsule strips readily, its stellate veins are injected, its cut surface may be bloody, is of a deep-red color, and its glomeruli are prominent. This is the condition generally described as "cyanotic induration." Should this state be long continued, a slowly produced fibrosis is the result, which, although rarely great in degree, may yet suffice to produce contraction and consequent lessening of the size of the kidney, giving it the characters of a diffuse nephritis.

A passively congested kidney excretes a less amount of water than normal; the urine, therefore, is scanty, and for this reason of high specific gravity, highly colored, and readily precipitates its urates. Albumin is likely to be present in small quantity, and casts in number commensurate with the destruction of epithelium; the latter being very gradual, casts are generally few.

It will be obvious to the practitioner that this condition of affairs is not easy to differentiate from an early nephritis; even the result of rest in a rapid clearing up of the signs and symptoms may not be sufficient to make the diagnosis plain; nevertheless, the recognition of the existence of a cause for the congestion may assist. But it is to be remembered that there is no marked fundamental difference between the pathological results brought about by the one and the other; in fact, as stated above, when contraction has occurred as a result of long-continued congestion, we have practically a state of diffuse nephritis. During all the time that this process has been in progress, the causative factor, such as cardiac disease, should have engaged attention, and the renal changes should have been recognized as merely a resultant part. To consider the latter as a separate feature is a distortion of perspective that ought not to be encouraged; hence the absence from these paragraphs of any discussion of treatment.

Thrombosis of the Renal Vessels and Infarct of the Kidney.—Thrombosis of the renal vessels, either artery or vein, or both, may occur. More than half a century ago it was recognized that the left renal vein of marantic infants was frequently the seat of thrombosis; the greater length of the left vein appeared to render it more prone to the process than the right. Thrombosis of the renal, as well as of other veins, was considered to be a sequence of a cachectic state, and to-day we can add little more to this than to point out the probability of its being the direct outcome of an infection that generally proves to be terminal. The appearance of such a kidney, and the existence of symptoms or signs resulting therefrom, will depend largely upon the perfection of the collateral circulation; if the process does not prove fatal, the thrombosis will be found to have brought about a state of affairs not widely different from that found in passive hyperæmia of the organ. Diminution of the urine, its high color, the presence in it of hæmoglobin, and an icteroid tint of the skin are the external results that may be expected.

Thrombosis of the renal artery may occur from trauma or from disease of the wall of the vessel, but is rarely found. If the entire vessel be occluded, complete and rapid necrosis of the kidney results. Much more commonly, embolism of a branch of the renal artery, with its resultant thrombosis, is seen. Emboli may be infective or non-infective, according to the nature of the

original process from whose site the embolus is derived. In the former case there is a metastatic abscess set up in the area concerned; in the latter, the well-known infarct is formed.

An infective embolus can and frequently does cause an infarct, but the rapid progression of the bacterial process causes the picture to be dominated by the features of abscess formation. When the embolus is non-infective, the case becomes one of infarction pure and simple. Such emboli are set free most often from thrombi or vegetations in the left side of the heart, but may happen when any foreign body, such as a mass of tumor cells, finds its way into the arterial circulation. Whatever be the appearance of such an infarct immediately after its formation (and this is still a subject of debate), when seen the lesion is a yellowish, sometimes golden, roughly triangular area, edged by a hyperæmic zone of kidney substance; if superficial, it usually projects slightly from the level of the kidney, and is as prominent on the external as on the cut surface of the organ. Sometimes the cortex is infarcted in its entirety, as occurred recently in an eclamptic kidney from the laboratory of the Royal Victoria Hospital;[1] the medulla and the contiguous layer of cortex were spared, since the thrombosis had occurred in the interlobular arteries. All but the largest infarcts become replaced by fibrosis and ultimately are represented by depressed scars on the outside and fibrosed scars in the substance of the kidney.

Except in the case of the largest infarcts, there is usually no symptom or sign of their formation; a sudden pain in the kidney, with the appearance of blood or hæmoglobin in the urine, in a patient prone to embolus, would justify the supposition that infarction had occurred; but usually, from the very fact that the primary disease is so serious, the existence of the renal infarct is unobserved; thus there is no need to deal with the question of prophylaxis or treatment, as these ends are served in the measures that are rationally adopted in the care of the primary disease.

[1] Klotz, *Journal of Obstetrics*, October, 1908.

CHAPTER III.

ANOMALIES OF URINARY EXCRETION.

By A. E. GARROD, M.D., F.R.C.P. (Lond.).

The changes observed in the properties and composition of the urine in disease are almost infinite in their variety. Some are obvious to the most casual observer, gross deviations from the normal in tint, specific gravity, or volume. Others are readily detected by means of such simple tests as form part of the routine of clinical examination. Others, again, are only brought to light by elaborate chemical methods, or by the employment of instruments of delicacy and precision, for the use of which special training is required. Many have doubtless escaped detection up to the present time.

When the kidneys are the seat of disease the impairment of their functions may be manifested by imperfect excretion of urinary ingredients, of inorganic salts, or of the end products of protein metabolism. The urinary water may be greatly diminished in quantity, or may be much in excess of the normal amount.

The impairment of function may also be revealed by diminished molecular concentration of the urine, whilst that of the blood is increased to a corresponding extent. It may also be demonstrated by the effects of injection of colored substances, such as methylene blue.

Diseased kidneys may allow passage to the normal proteins of the blood, which it is one of their chief functions to retain in the circulation whilst allowing passage to waste products. Hence, albuminuria comes to be one of the most important of the signs of renal disorders.

Lastly, products of the breakdown of renal structures, such as epithelial cells and tube casts, may bear witness to profound changes of which the kidneys are the seat.

Such changes as the above, indicative of disease of the urinary organs, constitute only a small proportion of the deviations from the normal which are met with in disease.

Anomalies due to metabolic derangements, in which the kidneys are in no way primarily concerned, are very numerous, and often quite as conspicuous. Hence, the condition of the urine comes to reflect the state of the organism as a whole.

In the present article the above two classes of urinary indications will be discussed separately, as far as is possible. This plan has certain obvious advantages when the subject is treated from a clinical standpoint, but seeing that the same anomaly may be due in one case to disease of the urinary organs and in another to disease behind the kidneys, it cannot be fully carried out without needless repetition.

CHANGES IN THE URINE DUE TO DISEASES OF THE KIDNEYS AND URINARY TRACT.

Polyuria and Ischuria.—Variations in the quantity of urine excreted are important signs in some varieties of renal disease. For clinical purposes the collection of the total urine of twenty-four hours is always desirable. By its means only is it possible to check the statements of the patients, who are apt to mistake too frequent calls to micturition for polyuria. For the purpose of quantitative estimations such collection is essential, and even for qualitative testing it is desirable that the specimen examined should be a fair sample of the day's total. Thus, in not a few cases of granular kidney albumin is absent from some isolated specimens, and in cases of alimentary glycosuria *ex amylo*, sugar may only be present after a carbohydrate meal.

Diseases of the kidneys may give rise to polyuria on the one hand, or to ischuria on the other. The ischuria, which may even amount to complete anuria, of acute nephritis may afford an even better indication of the degree to which the excretory function of the kidneys is impaired than do the amounts of albumin and blood which the urine contains. The polyuria of granular kidney is a familiar sign; and of scarcely less clinical significance is the development of polyuria, with abundance of albumin, in cases of parenchymatous nephritis which are entering upon a chronic stage.

Whereas, the destruction of one kidney or the blockage of its ureter does not profoundly or lastingly affect the volume of the urine, obstruction of the second ureter, or the simultaneous blockage of both, causes a form of anuria of great interest, on account of the nature of the symptoms which result, and of great clinical significance as urgently calling for surgical intervention.

The intermittent passage of large quantities of urine, simultaneously with the disappearance of a renal tumor, is a valuable diagnostic sign in cases of unilateral hydronephrosis in which the kidney has become dilated, so as to form a large sac the contents of which are discharged at intervals.

In basing any conclusions upon the volume of urine it is important that its density be taken into account. Thus, scanty urine of low specific gravity may serve as a valuable sign of threatened uræmia, whereas abundant urine of high specific gravity is suggestive of diabetes rather than of renal disease.

Specific Gravity.—Just as inferences based upon the volume of the urine are of little value unless the specific gravity is taken into account, the information which the specific gravity affords needs to be supplemented by a knowledge of the quantity excreted, in order that any satisfactory conclusions may be drawn from it. Moreover, seeing that the specific gravity varies widely at different periods of the day, it is important that the specimen tested should, if possible, be a sample from the day's total. The specific gravity affords a measure of the proportion of solids in solution, and deviations from the normal density, about 1.020, may result from excessive or deficient excretions of water or from variations in the output of dissolved substances.

In the employment of the ordinary urinometer certain points of detail call for attention if accurate results are required. The instrument itself

should have been tested and found to give accurate readings at ordinary temperatures. The containing vessel should be of adequate diameter, so that the influence of capillary attraction does not come into play, and into it the urine should be gently poured so that frothing is avoided. The urine should have cooled to the temperature of the air, and the urinometer should be allowed to sink gently into the liquid so that unnecessary wetting of the index stem may be avoided. The reading should be taken from the lower meniscus. Unless calculated for a normal volume of urine a low specific gravity does not imply a diminished output of solids in solution, for in association with polyuria there may be a daily output of excretory products which is in no way below the average, although, as in diabetes insipidus, the specific gravity may be very low. Even if the reading be low when corrected for a normal volume of 1500 cc. allowance must be made for the nature of the patient's diet and the amount of protein which it contains.

However, in renal cases the indications which the urinometer affords are often of much value, as, for example, when, apart from any increase in the volume of urine, the specific gravity tends to fall; as it often does before the onset of uræmic symptoms. In this connection it must not be forgotten that in the late stages of many maladies of chronic course, but in which the kidneys are not directly implicated, when death is approaching and the metabolic fires are burning low, urine of low specific gravity and scanty in amount is wont to be excreted.

Cryoscopy.—The method of cryoscopy, or determination of the freezing point, recently applied to clinical purposes by A. von Koranji, owes its importance to the fact that the depression of the freezing point of a solution supplies a measure of the osmotic pressure, and this again depends upon the number of molecules in solution. Thus, equimolecular solutions of two different substances will show a depression of the freezing point of equal degree, and when two or more substances are in solution the depression will correspond to the total number of molecules, irrespective of their nature.

In dealing with an organic liquid such as blood or urine the conditions are not so simple. Salts, such as sodium chloride, are dissociated into their component ions, and each ion, which counts as a molecule for the purpose in hand, has an equal effect upon the freezing point with a heavy protein molecule. In the case of the urine the most abundant constituents, and especially sodium chloride, are largely responsible for the observed depression.

Moreover, in the complex mixture, molecular re-arrangements occur after excretion, and these, as Koppe has shown, tend to diminish the numbers of effective molecules. The conversion of urea into ammonium carbonate will have a like effect, and therefore it would be desirable to make the determination with freshly passed urine, whereas the results will have little value unless a sample of the excretion of twenty-four hours be taken.

Again, the total number of molecules in a sample specimen will be largely determined by the bulk of the urine in the day, so that an unusually high freezing point may depend upon a copious excretion of water, as well as upon a diminution of the solid constituents in solution.

Accordingly, it is found that whereas the freezing point of the blood of healthy persons deviates but little from —0.56° C., that of their urine varies between —1.3° and —2.2° C. Chiefly on this account the indications afforded by cryoscopy of the urine alone, in cases of bilateral renal disease, are apt to be inconclusive as to the functional competency of the kidneys.

When the freezing point of the blood can be compared with that of the urine in such cases the results obtained have a much greater value. The accumulation of excretory products in the blood lowers its freezing point, whereas their comparatively scanty presence in the urine has an opposite effect, and the two figures tend to approximate. In extreme cases the freezing point of the blood may be equal to, or even lower than, that of the urine.

In acute nephritis, as Lindemann has shown, recovery is accompanied by a progressive fall of the freezing point of the urine until normal figures are once more reached.

To the surgeon the method of cryoscopy may prove of much value by affording indications of the relative integrity of the two kidneys in cases of unilateral disease, when the urine from each kidney can be obtained separately by means of the separator or by catheterization of the ureters.

In determining the freezing point Beckmann's apparatus, or some modification thereof, such as the pektoscope of Zikel, is employed. The urine is placed in a wide test tube closed by a cork with two bores. Through one opening passes the thermometer, the bulb of which lies in the liquid, and through the other a metal stirrer, by means of which the liquid is kept in constant movement during the determination. The tube is enclosed in a second larger test tube and is held in place by a washer around its neck. It is thus surrounded by a jacket of air which insures the equal cooling of all parts of the contained liquid. The whole apparatus is placed in a freezing mixture contained in a beaker of suitable size. The thermometer used registers temperatures between $+1°$ and $-4°$ C., and is graduated to hundredths of a degree. As the urine is cooled the mercury column of the thermometer immersed in it steadily falls until the freezing point is approached; a rise then occurs, and the highest point of this rise is the required freezing point.

Electrical Conductivity.—The determination of the electrical conductivity of the urine affords another means of determining the number of contained ions. Here again sodium chloride plays the most important part in causing variations in the resistance offered. Molecules which are not dissociated do not favor conduction, and a urine of high specific gravity, due to contained sugar, may, nevertheless, have a high resisting power. Hence the indications afforded by electrical conductivity are different from those afforded by the freezing point.

Other Tests of Functional Competency of the Kidneys.—Reference must here be made to some methods of testing the integrity of the kidneys which depend upon the injection of pigmentary and other substances.

Of these the methylene-blue test is the best known. An intramuscular injection is made of 1 cc. of an aqueous solution of methylene blue (1 in 20), and specimens of urine are collected at intervals of half an hour, one hour, and afterward hourly, until the pigmentation is no longer appreciable. The points to be noted are (1) the time at which the pigment first appears in the urine, (2) the time of maximum excretion, and (3) the time when the excretion stops. In normal individuals excretion of the pigment begins one hour after the injection, or a slight tinting may be observed even after half an hour. The maximum is reached in three to four hours, and is followed by a gradually diminishing excretion lasting from thirty-six to sixty-four hours from the injection. Absence of pigment after one hour, a maximum delayed beyond four hours, and tinting of the urine for as long as five or six days

are held to indicate defective eliminating power of the kidneys. As some of the pigment is apt to be converted into chromogen, control specimens should be warmed with acetic acid. Rosaniline, sodium salicylate, and potassium iodide have been similarly employed as test substances.

The glycosuria which is induced by phloridzin is believed to be due to an action on the renal epithelium, and the excretion of sugar has been found to be hindered by disease of the kidneys. A test based upon this is carried out as follows: 1 cc. of a 1 in 200 solution of phloridzin (containing 0.005 gram) is injected subcutaneously, or into a muscle, after the patient has emptied his bladder. In normal subjects sugar appears in the urine after from half an hour to an hour, and disappears after two to four hours. The total excretion amounts to 1 to 2 mg. In disease, the quantity of sugar excreted may be much less or no glycosuria may result. This is a test of the integrity of the renal epithelium and not of the permeability of the kidneys. The value of the phloridzin test is much diminished by the fact that even in normal subjects the amount of glycosuria induced varies within rather wide limits.

Reaction of the Urine.—This may afford valuable indications as to the condition of the urinary tract, but here again variations may equally result from conditions above the kidneys. Alkalinity due to the presence of ammonia and ammonium carbonate points to infection of the bladder or urinary passages, seeing that it is due to the decomposition of urea under the influence of bacteria. It is a prominent symptom of cystitis. It must be remembered, however, that certain microörganisms produce pyelitis or cystitis with acid urine.

Ammoniacal urine may be recognized by its peculiarly offensive smell and by the change to blue of moistened red litmus paper held above the surface of the liquid. Alkaline urine of this character deposits abundant crystals of ammonio-magnesium phosphate, and since it is usually associated with cystitis, many leukocytes are, as a rule, present in the sediment, and the urine may swarm with bacteria.

Albuminuria.—One of the most important of the renal functions is that of refusing passage to the proteins of the blood, whilst allowing a free passage to the end products of metabolism. This function appears to be a highly specialized one, for proteids foreign to the blood, unless present in very small quantities, are not held back to at all the same extent, as witness the free excretion of hæmoglobin in the paroxysms of hæmoglobinuria, and of the Bence-Jones protein by kidneys which are not the seat of disease.

With serum albumin, the blood globulin, and fibrinogen the case is different, and although there are grounds for believing that minute quantities of these substances find their way even into normal urines, and that, occasionally, amounts appreciable by ordinary clinical tests pass through kidneys which are not seriously abnormal, in the conditions included under the name of functional albuminuria, the fact remains that the continuous excretion of appreciable quantities of albumin usually denotes renal disease, either primary or secondary to circulatory disturbances. Hence, albuminuria comes to be the most important of the urinary signs of disorders of the kidneys, and has a wholly different significance from the excretion of other protein substances in the urine.

Although it may be accepted as proven that the albumins of urine are actually blood proteids which are not held back as they should be, the

relative proportions of serum albumin and globulin are by no means those which prevail in the blood. Serum albumin usually preponderates greatly in the urine, but globulin is usually also present in varying amounts. Whereas, serum albumin alone may be present, this is hardly ever the case with globulin. The results of the investigations which have been carried out with a view to determining the significance of the relative proportions of the two proteids in albuminous urine have not proven of much clinical value. The most recent investigator in this field, J. Joachim, has confirmed the statement of others that in cases of lardaceous disease of the kidneys the proportion of globulin in the urine is markedly higher than in other forms of renal disease in which albuminuria occurs, and this increase proves to be wholly of the euglobulin fraction. Moreover, it would seem that a low proportion of globulin in cases of nephritis is a favorable indication. Halliburton suggests that, speaking generally, much globulin indicates a grave renal lesion. Further than this our present knowledge does not allow us to go.

Considerable interest attaches to that protein of urine which is precipitated by the addition of dilute acetic acid to the diluted or undiluted urine in the cold. That this is not mucus, as was originally thought, was shown by the fact that when treated with mineral acids it yields no reducing substance, and for many years it was looked upon as nucleo-albumin. K. A. H. Morner more recently arrived at the conclusion that this substance was in reality composed of compounds of serum albumin with chondroitin-sulphuric acid, nucleic acid, and, in cases of jaundice, with taurocholic acid. Still more recently it has been stated by A. Oswald that the protein so precipitated from albuminous urine in cases of nephritis and of cyclic albuminuria is a mixture of euglobulin and fibrinogen. The more recent work seems to prove that this substance is derived from the blood and is not a product of the diseased renal epithelium. Its presence has, therefore, a like significance to that of serum albumin and globulin.

In considering the clinical significance of albuminuria it is necessary to draw a sharp distinction between the true renal forms and what has been styled accidental albuminuria. The mere presence of albumin in the urine does not necessarily imply a renal origin. In some cases it results from the admixture of vaginal discharge or of semen, in others it is due to disease of the urinary passages. Urine which contains blood or pus must always yield the reactions of albumin, and albumin is also present in chylous urines.

Physiological or functional albuminuria offers a problem of no small difficulty, upon which the last word has by no means been said. It may be taken as proven that minute quantities of albumin, so minute that they escape the ordinary tests, are present in normal urines. Somewhat larger amounts are not uncommonly met with apart from any other signs of organic renal disease. The frequency of this condition has been variously estimated by different observers, and in weighing such statistics it is important to take into consideration the nature of the tests employed, whether the presence of albumin is demonstrated by such reactions as the heat and the cold nitric acid tests, or only by such extremely delicate reagents as salicyl-sulphonic acid.

It is not difficult to imagine that the retentive power of the renal filter may vary in different individuals, and that in some it is so far imperfect as to allow of a certain leakage of the blood proteids, which can be detected

by ordinary tests, apart from any state which can be strictly described as pathological. Clinical experience teaches us that it is not uncommon for small quantities of albumin to be present in the urine of patients who are for the most part young, and who are often boys, who nevertheless exhibit no other signs of renal disease. Such albuminuria may be temporary or intermittent, and it is not proven that its subjects are especially liable to develop renal disease in later life. What is chiefly to be desired is a more complete knowledge of the after-history of such cases. No doubt in some instances what seems to be a functional albuminuria is in reality a sign of interstitial nephritis developing at an unusually early age, but in such cases cardiovascular changes will manifest themselves sooner or later.

Some subjects of functional albuminuria excrete albumin only after exertion, others after a cold bath, and others after mental or bodily strain. Severe and prolonged exertion will induce albuminuria in many persons. Often, as Pavy pointed out, the functional albuminuria is profoundly influenced by position, and may only be present during the active hours. However, the influence of posture is also well-marked in cases of albuminuria due to gross renal lesions.

That the excretion of albumin in quantities easily detected is not strictly normal is an obvious truism, but the evidence is strong that it may be a symptom of no serious significance. Our interpretation of the observed facts will depend largely upon the views which we hold as to the limits of idiosyncrasy as distinguished from disease. A few such cases carefully watched from childhood to advanced life would throw more light upon the question than many investigations covering only brief periods.

The so-called alimentary albuminuria, such as follows the copious taking of raw egg albumen, does not belong to the same category. It has been shown by precipitin tests that in such cases much of the protein excreted is egg albumen, which may be regarded as a protein foreign to the blood, for which proteins the kidneys have a less retentive power. However, in respect to such albuminuria idiosyncrasy appears to play an important part.

Albuminuria due to circulatory disturbances is a common symptom, well exemplified in cases of cardiac disease in which compensation fails and backward pressure leads to passive congestion in the kidneys. It is uncertain how far the increased pressure is directly responsible for the escape of albumin under such conditions, but it seems certain that the main cause is a secondary change in the renal epithelium due to deficient conveyance of oxygen to the part. When there is a complete obstruction of the renal vessels, as the result of embolism or thrombosis, the necrotic changes in the infarcted area amply account for the albuminuria which results. The albuminuria of cholera has been ascribed to deficient blood supply to the kidneys, but toxic influences probably play an important part in its causation.

In the *albuminuria of fevers*, which constitutes a well-defined variety, circulatory disturbances may also come into play, but it is probable that a mild form of toxæmic nephritis is often produced, and the cloudy swelling, so often seen at autopsy, bears witness to the changes in the renal parenchyma which fevers induce. This view gains in probability from the observation that the duration of the fever, rather than its intensity, is the most important factor in determining the excretion of albumin.

Albuminuria of slight degree is a common symptom in *jaundice*, and here also it is presumably toxic. Hyaline casts are usually present in considerable

numbers, even in cases of jaundice in which no albumin is to be detected by the ordinary tests. Graver varieties of *toxic nephritis* are caused by various poisons, such as cantharides, turpentine, and carbolic acid.

Special interest attaches to the albuminuria which is associated with nervous disturbances, the pathology of which is obscure. The temporary presence of albumin in the urine after epileptic fits, which has occasionally been observed, has been compared with that which is sometimes induced in healthy subjects by violent muscular exertion.

The albuminuria which results from *gross lesions of the kidneys* is the most important of all. The quantities of albumin excreted vary very widely from the conditions met with in acute parenchymatous nephritis, and in many chronic cases of the same disease, in which the urine becomes almost solid on boiling, to the no less significant presence of mere traces, in association with granular kidneys. However, in cases of granular kidney in which the heart is beginning to fail the amount of albumin in the urine may be very greatly increased.

Detection of Albumin in Urine.—The tests most often employed in clinical work are the heat test and the cold nitric acid test. Although they are far from being the most delicate available it may safely be stated that any quantity of albumin which they fail to reveal may, for ordinary clinical purposes, be neglected.

In performing the heat test the urine, if at all turbid, should be filtered, and the upper portion of the column in the test tube should be boiled. If a turbidity appears this may consist of albumin or of earthy phosphates thrown down as a result of a re-arrangement of bases produced by boiling. On the addition of a drop or two of acetic acid the cloud will disappear if it be due to phosphates, but if albuminous will persist or increase in density. When much albumin is present the coagulum will collect together and become flocculent when the acid is added.

Urines containing traces of albumin may show no turbidity on simple boiling, but if they be again boiled after the addition of acetic acid a cloud may appear. This second boiling should, therefore, always be carried out. For the detection of slight turbidity the test tube should be held before a dark surface.

In many albuminous urines, turbidity is produced when acetic acid is added in the cold, especially if the urine has been previously diluted with water. This is the precipitate of euglobulin and fibrinogen which has been referred to already. Precipitates of urates similarly produced will clear on warming; they will not appear after dilution of the urine.

The advantage of the heat test lies in the fact that it is not yielded by other proteins than serum albumin and globulin. The only other urinary protein precipitated by heat is the Bence-Jones protein, but this is distinguished by the fact that the liquid clears almost completely as the boiling point is approached, especially if acetic acid has been added. The precipitate of earthy phosphates will hardly lead to mistakes, as acetic acid should always be added as a routine proceeding.

Heller's test with cold nitric acid is best performed as a ring test. The nitric acid and urine are placed in separate test tubes, and with the tubes inclined to each other at a very wide angle the urine is allowed to flow very gently on to the surface of the acid. If albumin be present an opaque white ring, or rather disk, appears at the junction of the liquids. Beneath

it a colored layer is often seen, due to oxidation of indican. When very minute traces of albumin are sought for it is well to employ a wide test tube or a small beaker. A faint, hazy ring above the junction of the liquids is due to the protein which was formerly spoken of as nucleo-albumin. In concentrated urine a ring of uric acid may form, which disappears on warming, and is not obtained after dilution of the urine. After standing for a short time a crystalline ring of nitrate of urea is formed if the urine tested be very concentrated. Another possible source of error is the precipitation of resins, such as copaiba, in the urine of patients taking such drugs. Other proteins, such as the Bence-Jones albumin and albumoses yield this test as well as serum albumin and globulin.

A number of different test solutions are also employed for the detection of proteins in urine. These all precipitate albumoses in addition to albumin and globulin, but the albumose precipitates disappear on heating, to reappear when the liquid is again cooled.

Of these, a saturated solution of picric acid is often used, either as a ring test or by the addition of the urine to the test solution. Care must be taken that the reagent is in excess. A solution of potassium ferrocyanide is widely employed, after acidification with acetic acid. Trichloracetic acid may also be mentioned, and salicyl-sulphonic acid, which is one of the most delicate and satisfactory of the precipitants of proteins; and only proteins are precipitated by this reagent. A few drops of a saturated solution of salicyl-sulphonic acid are added to the urine in the cold. If a turbidity results the liquid should be heated, when the turbidity, if due to an albumose, will disappear.

The presence of globulin in considerable amount may be demonstrated by Sir William Roberts' test. The urine is allowed to fall, drop by drop, into a beaker of distilled water. If much globulin be present the path of each drop is made visible by the formation of a milky turbidity, for such proteins are insoluble in distilled water.

A very rough notion of the proportion of albumin present in urine may be obtained by boiling a specimen in a test tube after the addition of a drop of acetic acid, and estimating the relative depth of the coagulum after it has had time to settle. By the use of Esbach's albuminometer a much more accurate notion may be obtained which suffices for ordinary clinical purposes, such as the estimation of the progressive diminution of albuminuria during recovery from acute nephritis. When this method is employed allowance must be made for variations in the total quantity of urine excreted.

The albuminometer consists of a stout test tube, with a stand upon which it rests in an upright position. Graduations on the side indicate the height to which the tube should be filled with the urine, and the amount of reagent to be subsequently added. Smaller graduations from 1 up to 7 indicate, by measuring the height to which the precipitate reaches, the quantities of albumin per mille.

The reagent is prepared by dissolving 10 grams of picric acid and 20 grams of citric acid in a liter of water. The urine, if alkaline, should be rendered acid with acetic acid, and if it be rich in albumin should be diluted by the addition of a known proportion of water.

Urine having been placed in the tube up to the line marked U, and reagent having been added to that marked R, the tube is closed with an india-rubber

cork and is gently inverted several times, with avoidance of shaking. After it has stood for twenty-four hours the height of the precipitate is read off. The readings should be taken at fairly constant temperatures, and any dilution must, of course, be allowed for.

Among other approximate methods that of Roberts and Stolinkoff may be mentioned; this depends on the fact that the greater the amount of albumin present, the sooner will a ring appear with the cold nitric acid test. In a number of test tubes, specimens of urine diluted to various extents are poured from pipettes upon the surface of nitric acid. That dilution at which the ring appears in from two to three minutes is taken as the standard, and from it, by means of a simple formula, the percentage of albumin in the original urine can be calculated.

For accurate determinations, either of the total albumin or of serum albumin and globulin separately, it is necessary to proceed by laboratory methods, the proteins being isolated from the urine, dried and weighed.

Sediments Indicative of Disease in the Urinary Tract.—The microscopic examination of urinary sediments often supplies important information as to the presence of morbid conditions in the kidneys or urinary tract.

Normal urine is clear and limpid when passed, but on standing a slight cloud develops in the liquid, which is known as the nubecula; this may lie at the bottom or may hang suspended in the urine. The position is in part determined by the specific gravity of the liquid and in part by the inclusion of air bubbles.

The bulk of the nubecula consists of urinary mucoid, and in it are entangled a few epithelial cells, the sheddings of the surface layers of the mucous membrane, and also a few leukocytes. Seeing that, with the exception of bacteria, no cellular elements can pass the renal filter, any such which are present in the urine are derived from the kidneys themselves, or from the urinary passages, bladder, or generative organs. A few squamous epithelial cells may be looked upon as normal urinary constituents; only when the cells are numerous, and bear signs of coming from the deeper layers of the mucous membranes or from the renal tubules, can they be regarded as indicative of disease.

Red blood corpuscles afford the sole criteria of hæmaturia as distinguished from hæmoglobinuria, and their presence, even in small numbers, is evidence of hemorrhage from the kidneys or below. After soaking in urine they lose their hæmoglobin and their biconcave form, and become globular or crenated.

Leukocytes may be derived from vaginal secretion, and the presence of a few such cells has no serious import. In cystitis they may occur in any numbers, and when suppuration occurs in the kidneys or any other portion of the tract. The presence in them of gonococci is naturally of prime diagnostic importance. In alkaline urines they are apt to be swollen, globular and hyaline, and their nuclei may only be demonstrable by the addition of acetic acid. When, as is sometimes the case, it is difficult to distinguish the leukocytes from cells from the renal tubules, the far deeper staining which iodine imparts to the former may be employed as a test.

The epithelial cells which are met with in urine are of different shapes and sizes, and from their characters some indication may be obtained of the parts from which they are derived. However, even to the trained eye, the exact determination of their place of origin presents no small difficulty,

especially when, as is often the case, they exhibit degenerative changes which alter their appearance and forms.

The cells shed from the surface layers are usually of the flat varieties. Exceptionally large squamous cells, often adherent into groups, are derived from the mucous membranes of the vulva, vagina, and prepuce. Of the true urinary epithelial cells those from the bladder are the largest. Tailed, pyriform, and oval cells are derived from the deeper layers and therefore suggest a more deep-reaching affection. They may come from the bladder, prostatic urethra, or pelvis of the kidney. The small, rounded, or polygonal cells, with well-defined nuclei, which are derived from epithelium of the renal tubules, are the most important from a diagnostic standpoint, and if abundant they afford evidence of renal disease hardly less convincing than that derived from the presence of renal casts. Not merely the presence but also the condition of the epithelial cells is of importance. Some changes are merely due to their being soaked in the urine, but the presence of fat globules in their protoplasm may serve to give an idea of the degree of the morbid process at their place of origin.

Renal Casts.—These owe their importance to the fact that, being obviously formed in the renal tubules, their presence in any considerable numbers indicates that all is not well with the kidneys; and that when albumin or blood is also present the albuminuria or hæmaturia is of renal origin.

The evidence of their renal origin is conclusive. In shape and size they correspond to the renal tubules, and they are often bedecked with epithelium which is obviously renal. Moreover, in sections of diseased kidneys they are frequently seen in situ. However, it cannot be inferred from the presence of a few hyaline or stippled casts in a centrifugalized deposit that anything serious is amiss with the kidneys. A few such objects may be found in some otherwise normal urines if the centrifuge be employed, and the almost constant presence of such casts in cases of jaundice suggests an irritant action of the bile constituents in the circulation upon the renal epithelium. Of renal diseases, it is in those which specially implicate the renal parenchyma that casts are most numerous, whereas in cases of granular kidney they are scanty or absent.

Hyaline casts are very delicate structures, so transparent that they may be difficult of detection in unstained specimens. The material of which they are composed is undoubtedly protein in nature, but when the scantiness of the material available is considered it is not surprising that its exact nature is not certain. Two chief views have been advocated; on one they are regarded as composed of a secretion of the renal epithelium; on the other as consisting of albumin which has coagulated and has subsequently undergone a hyaline change. Such casts vary greatly in length and often have broken ends, indicating that they originally formed parts of longer specimens. It would seem that hyaline casts often indicate the slightest degree of renal mischief or the incipience of graver troubles. They are usually abundantly present in the early stages of acute nephritis, but even in the most chronic cases of parenchymatous nephritis they are met with in association with casts of various other kinds.

Epithelial casts are considerably larger than the hyaline, as is natural, seeing that the former correspond in size to the lumen of the renal tubule, whereas the latter represent the size of the tubule stripped of its epithelial

lining. Every stage is met with, from a hyaline cast with a few cells from the tubal epithelium attached to it, to those which apparently consist wholly of epithelial cells, or from which a bare hyaline core may project at one end. Such objects are seen in their most perfect forms in the early days of an acute nephritis, and the cells with which they are clothed may have a cloudy or swollen appearance. Later on the condition of the epithelial cells may bear witness to a more advanced stage of disease; they may have a granular appearance, or may even contain highly refractive fat globules.

The so-called *amyloid or waxy casts*, larger and less transparent than the hyaline, but homogeneous and often showing partial segmentation, are believed by many to be derived from those of the epithelial variety by degeneration and fusion of the constituent cells. Although they sometimes show the red coloration with methyl-violet and stain deeply with iodine, their presence affords no evidence that the kidneys from which they come are lardaceous. They indicate rather an advanced and chronic renal trouble, and are most often met with in cases of chronic parenchymatous nephritis of somewhat long standing.

The casts which are grouped together under the name of *granular* differ considerably in appearance and size. Some are narrower and some broader; the component granules may be larger or smaller in size. They are opaque objects, and often have a brown tint. That they are friable is shown by the fact that they are usually short and often show broken ends. It is believed that the granules arise from the disintegration of epithelial cells, and they are therefore held to indicate somewhat advanced renal lesions. They are met with in the urine in all varieties of nephritis and a few may be present in cases of granular kidneys. In cases of chronic parenchymatous nephritis a large proportion of the casts present are usually of this nature. Transitional stages between epithelial and granular casts are not infrequently met with.

Fatty casts are held to denote an advanced degeneration of the renal epithelium. Fat granules, recognized by their high refractive power, are sometimes present in the cells of which epithelial casts are composed. In many granular casts some of the granules are composed of fat, and occasionally the casts are mainly composed of fat globules. Acicular crystals of fat or of fatty acids sometimes project from such casts, usually from one extremity, and impart a hedgehog appearance.

Among other varieties, hyaline casts studded with red blood corpuscles or crystals of calcium oxalate are sometimes seen. Casts richly beset with red corpuscles are common in the early stages of acute nephritis. Leukocyte or pus casts are much less common, as also are such as are composed of bacteria.

The so-called *cylindroids*, long hyaline objects with tapering ends which often show a wavy outline and longitudinal striation, are threads of mucus which have no connection with true renal casts. Other objects which simulate renal casts are composed of amorphous urates or of hæmoglobin debris which have assumed cast-like forms.

Spermatozoa must also be mentioned among objects found in the sediment. Their presence will sometimes explain a slight albuminuria, and deprive it of any import as a sign of renal trouble.

The presence in the sediment of the ova of *Bilharzia hæmatobia* will afford conclusive evidence in cases of the endemic hæmaturia of some parts of Africa. Within the oval envelope with its lateral or terminal spine

the ciliated embryo is visible, and sometimes makes its escape from the shell under observation. The presence of hydatid hooklets which are easily recognized by their characteristic form, or of scolices, reveals the presence of hydatids in, or in connection with, the urinary tract; and the *Filaria sanguinis hominis* has sometimes been found in the urine.

Hairs are usually accidental additions, but when a teratoma communicates with the tract hair is sometimes passed in considerable quantities, the phenomenon being known as *pilimictia.*

Crystalline Sediments.—It will be convenient to consider in this place the crystalline urinary deposits, for although their presence is usually dependent upon processes behind the kidneys, they may afford valuable clues as to the nature of a calculus or gravel, the presence of which is indicated by other symptoms. The various crystals have very different degrees of diagnostic value. Thus, whereas the presence of hexagons of cystin is the diagnostic sign of cystinuria, and renders it almost certain that symptoms of calculus are due to cystin stone or stones, other crystals such as those of phosphates indicate little more than an abnormal reaction of the urine, and those of triple phosphate suggest ammoniacal decomposition. It is a matter of no small importance whether the crystals are already present in the urine when it is passed, or merely separate when it is allowed to stand.

Uric acid crystals are the commonest of all those met with in urine. They are always tinted, although sometimes very faintly, by included urinary pigments. The pigments also play an important part in modifying the shape of the crystals. To urochrome is due the ordinary golden-yellow tint and the familiar whetstone form which they so often assume. Uroerythrin, if present, always contributes to the coloration, and to it is due the dark red color of "cayenne pepper sand." In carboluria the uric acid acquires a deep brown color, and the crystals appear black when seen in bulk. Those deposited from bile-stained urines are colored by the bile pigments, and when biliverdin is present are grouped into rosettes of greenish-yellow prisms. The exact conditions which determine the deposition of crystalline uric acid are not fully known. Klemperer assigns much importance to scantiness of urochrome; acidity certainly plays a part, as also does the amount of uric acid present, although excessive output of uric acid can by no means be assumed from the deposition of crystals.

The forms assumed are various; many are derivatives of the whetstone shape and some approach to dumb-bell forms. In the urine of young infants closely woven mats of minute whetstone crystals are sometimes seen, but it would seem that the formation of tiny spherules, with radiating crystalline structure, is the earliest stage of calculus formation. Many persons whose urine deposits abundant uric acid crystals never show any symptoms of calculus.

Crystals of *ammonium urate* are not infrequently deposited from feebly alkaline or amphoteric urines, often in company with those of ammonio-magnesium phosphate. Sometimes they assume the form of minute yellow dumb-bells or of the so-called "hedgehog crystals," small yellow spherules with sharp excrescences.

Calcium oxalate crystals are, next to those of uric acid, the commonest of all. They are often very minute, and form a snow-like layer on the top of the nubecula, or adhere to grease marks upon the sides of the containing glass. The commonest form is a flat octohedron, which appears, under the

microscope, in the semblance of a square envelope. Less common are cubical prisms with pyramidal ends. Twin crystals composed of interpenetrating octohedral forms are also seen. Imperfectly crystalline forms are sometimes present, such as oval disks with deep central grooves upon their flat surfaces, somewhat resembling avian red blood corpuscles, and more rarely true dumb-bells. When deposited from bile-stained urine, crystals of calcium oxalate are faintly tinted by bilirubin or biliverdin.

Ammonio-magnesium or triple phosphate is deposited in crystalline form from any urine which is undergoing ammoniacal decomposition, and the presence of such crystals has no greater significance than this. They assume various forms, of which the most characteristic is the familiar "knife-rest" or "coffin-lid" shape. Feathery forms are also met with. When the urine is frankly alkaline they are usually surrounded by a deposit of amorphous earthy phosphates, which, with the crystals, are easily soluble in acetic acid.

Neutral calcium phosphate or "stellar phosphate" forms crystals which are easily recognized and are not seldom seen in amphoteric urines and in those which owe their alkalinity to fixed alkalies. They form long, wedge-shaped prisms, with their broader ends cut off obliquely. They are usually grouped in stars, with their pointed ends toward the centre of the star.

Magnesium Phosphate.—In some forms of gastric disorder treated by large doses of magnesium carbonate, tabular crystals of normal magnesium phosphate have been met with in the urine. In a case of this kind Bradshaw found a sediment of long, narrow needles which he identified as consisting of acid magnesium phosphate.

Crystals of cystin are among the rarest of urinary sediments, but are present in all cases of cystinuria, although at times all the cystin may be held in solution. They form colorless hexagonal plates, the sides of which are often of unequal lengths, and groups of superposed hexagons are common. Long hexagonal prisms are sometimes present in association with the plates. They may be distinguished by their ready solubility in ammonia and also in hydrochloric acid. When a drop of concentrated hydrochloric acid is allowed to flow over dry cystin crystals, the hexagonal plates are replaced by rosettes of prisms which grow under the eye. These consist of cystin hydrochloride, and melt away again when the acid is diluted with water.

Xanthin crystals, which are always described among urinary sediments as lemon-shaped, and yellow in tint, have been met with in only a single case, described by Bence-Jones many years ago, and were only present in it for a day or two.

Calcium sulphate has been rarely met with as a sediment composed of long needles or tables with sloping ends; *calcium carbonate* is sometimes deposited from alkaline urines in small dumb-bells or spherules with concentric striation. *Calcium and magnesium soaps* in crystalline form, as needles resembling those of tyrosin, for which they may readily be mistaken, have been described by von Jaksch, and are sometimes seen adhering to and projecting from fatty casts.

Bilirubin or hæmatoidin, in the form of minute brown acicular crystals, may be found in urines containing bile, and in some cases of malignant disease of the kidneys or urinary tract in which old extravasations of blood

are breaking down. Crystals of these substances are indistinguishable from each other in appearance and probably are chemically identical.

Hippuric acid has been rarely seen as a urinary sediment composed of rhombic prisms.

Indigo blue is found in amorphous particles in many alkaline urines, and rarely in the form of crystals.

Crystals of tyrosin and leucin as urinary sediments will be described elsewhere.

In connection with disease in the urinary tract, *deposits of crystalline cholesterin* are of special interest, although they are very rare. The crystals may be very abundant, so that they appear as innumerable glistening particles when the urine is shaken. Under the microscope they have the characteristic form of rectangular plates each with one corner removed.

Satisfactory evidence is wanting of excretion of cholesterin by the kidneys as a result of its presence in excess in the blood, and it seems probable that, whenever met with, cholesterin in the urine has its origin in degenerative changes in the urinary tract. Some observations by Salisbury, recorded many years ago, seemed to support the contrary view, but his identification of the substance which he met with in urine as cholesterin was by no means conclusive, and Krusterstern failed to detect cholesterin in the urine of dogs after its intravenous injection in solution.

In chyluria, cholesterin appears in the urine in solution in the contained fat, and Beale found traces of this substance in cases of fatty kidney, by extracting with ether the collected sediments from large volumes of urine; these sediments consisted for the most part of fatty casts and shed renal epithelial cells.

The excretion of crystalline cholesterin has been observed in association with a variety of morbid conditions, all of which have this in common, that they are characterized by local lesions in the urinary tract. Thus, it has occurred in cases of congenital cystic disease of the kidneys, hydronephrosis, pyonephrosis, and chronic cystitis of long standing. Plaques of crystalline cholesterin have been found postmortem on the inner surface of the bladder and of the renal pelvis, and even in the substance of the kidney.

Lastly, calculi chiefly composed of cholesterin have occasionally been passed or removed from the bladder. These have usually been gallstones which have found their way into the urinary passages through bilio-urinary fistulæ, as was shown by the presence of bilirubin calcium, by facetting in some instances, or by the excretion of deeply bile-stained urine apart from any jaundice. No such explanation can be given, however, of a large calculus of almost pure cholesterin, described by Horbaczewski, which was removed by suprapubic lithotomy from the bladder of a little girl, and was mistaken for a cystin stone.

Hæmaturia.—Among the symptoms which indicate disease of the kidneys or urinary tract hæmaturia claims an important place. In many cases the diagnosis of the place of origin of the admixed blood, and of the cause of hæmaturia, presents little difficulty; in others both are extremely obscure. Whether the blood comes only at the beginning of micturition, or only at its end, or whether it is intimately mixed with the urine, are points which afford valuable aid. Again, cystoscopic examination or the use of the separator is often of the greatest use in diagnosis, as showing whether the blood comes from one ureter or from both, or has a vesical origin.

The microscope not only supplies the only certain means of diagnosing hæmaturia from hæmoglobinuria, a symptom of wholly different significance, but may also throw much light upon the origin of the blood. Thus, the presence of numerous casts, and their characters, will serve to locate the lesion in the kidneys, and may show whether we have to do with an acute lesion or with one of a more chronic kind. Again, detached epithelial cells, if present in considerable numbers and of characteristic forms, may serve to indicate the situation of a lower lesion. The presence of crystals of certain kinds in considerable numbers lends color to the view that the hæmaturia is due to a calculus, whereas the presence of many crystals of calcium oxalate is equally compatible with that form of hæmaturia which results from the free consumption of rhubarb. The mere fact that red corpuscles are the only objects to be detected in the sediment is of no slight clinical value in particular cases, in excluding some of the causes of hæmaturia.

Apart from the microscopic test, the tests for hæmaturia are mere indications of the presence of blood pigment as distinguished from blood. Urine containing blood necessarily yields the tests for albumin, and the negative results of such tests may exclude the presence of blood in cases in which the appearance of the urine suggests hæmaturia. On the other hand, the presence of an amount of albumin out of all proportion to the hæmoglobin strongly suggests a renal origin.

The color of the urine differs widely in different cases. It may resemble that of pure blood when the hemorrhage is copious, or a considerable sediment of blood may form on standing. When less blood is present it may impart a pink tint, or the urine may appear brown and smoky. The color may change from brown to pink on standing in contact with air. The brown tint is usually due to methæmoglobin, but occasionally a deeply brown-stained sediment contains the pigment in a peculiar insoluble form, whereas the yellow supernatant liquid fails to yield the tests for hæmoglobin. Alkaline urines containing blood have a peculiar livid tint in their deeper layers, shown by the spectroscope to be due to reduction of part of the dissolved hæmoglobin.

If the blood pigment in urine were always in the form of oxyhæmoglobin the spectroscopic test would be a very delicate one, but the band in red of methæmoglobin is not readily seen in very dilute solutions. In some cases of hæmatoporphyrinuria the pigment is in metallic combination, and shows absorption bands which may easily be mistaken for those of oxyhæmoglobin. When such urines contain albumin in small amount, the risk of mistake is much greater than when, as is usually the case, they are albumin-free.

Heller's test, by boiling the urine with liquor potassæ, is a delicate one, and when, after boiling, the color of the stained phosphate precipitate changes from brown to pink, and shows the spectroscopic bands of hæmochromogen, the presence of blood pigment is placed beyond doubt. It must be remembered that chrysophanic acid, which is present in the urine of patients taking rhubarb and senna, also tints the phosphate sediment deeply, but sediments so tinted show no distinct absorption bands.

The guaiacum and ozonic ether test is a very delicate one, provided that the reagents are freshly prepared. Under such conditions a negative result excludes the presence of blood pigment, and in practice the fact that other substances than blood cause the development of a similar blue color

will seldom mislead. The most likely cause of error is an iodide, taken as a drug, but unless the iodide be present in very large amount the blue color appears much more slowly than in urine containing more than minimal traces of hæmoglobin. To the trained eye the appearance of the urine affords as delicate an indication as any of the presence of blood pigment but confirmatory tests are of course essential.

The causes of hæmaturia are numerous. The blood may come from any part of the urinary tract, as the result of a variety of lesions. Thus, hemorrhage from the urethra may result from external injury, the passage of a calculus or gonorrhœa; the blood is passed at the commencement of micturition, being washed out of the urethra by the stream of urine. Prostatic hemorrhage is not uncommon in elderly men. Blood may come from the bladder in cystitis, when a calculus is present, or when its walls are the seat of tuberculous ulceration or of villous growths. In the vesical group may also be included the hæmaturia due to *Bilharzia hæmatobia*, and that of chyluria. Hemorrhage from the ureters may result from the passage of a calculus or from tuberculous ulceration, and to the same causes, as also to new-growths, may be due hemorrhage from the renal pelvis.

Renal hæmaturia has many different causes. In acute nephritis blood is almost always found in the urine, and in unfavorable cases the hæmaturia persists into the chronic stage. Copious hæmaturia occasionally results from granular kidney. In lardaceous disease it is not a prominent symptom, and is usually absent. Laceration of the kidney gives rise to copious renal hemorrhage. In renal tuberculosis hæmaturia is sometimes a prominent symptom, as also when the kidney is the seat of malignant growth. Infarction, if extensive, usually causes blood to appear in the urine. Among poisons, some, such as turpentine and cantharides, produce acute nephritis with hæmaturia.

Hæmaturia may occur in such diseases as purpura hemorrhagica, leukæmia, or scurvy, and also in the course of hæmophilia. In infantile scurvy hæmaturia of slight degree is a very common symptom, and may be the first to attract attention.

Certain less well-recognized and more obscure varieties of hæmaturia call for special mention. Crystals appear to be capable of causing hemorrhage by the mechanical effect of their passage. Uric acid crystals may produce this result in young infants, and even in adults calcium oxalate crystals have this power. In a not uncommon form of hæmaturia, which is alarming but without serious import, the excretion of blood and of numerous oxalate crystals is due to the copious eating of vegetables rich in oxalate. Of such rhubarb is the chief offender, but others may produce a similar result.

Far more obscure are certain cases of renal hæmaturia, which may be so copious as actually to threaten the life of the patients, but which are due to none of the causes enumerated above. The blood usually comes from one kidney, as is shown by cystoscopic examination, and in some instances nephrotomy has been performed, the kidney split open and no lesion found; yet after the operation the hæmaturia has permanently ceased. It is to such cases that the terms "renal hæmophilia" and "renal epistaxis" have been applied. In some such cases Hurry Fenwick has observed a dilatation of the vessels of a single papilla, removal of which has cured the hæmaturia, and microscopic examination of the part removed has revealed localized interstitial change.

Lastly, as clinical curiosities may be included some remarkable cases recorded by L. Guthrie and Attlee, in which hæmaturia, as an isolated symptom, has persisted for years in several members in two generations of a family who appeared to be otherwise in perfect health. Microscopic examination of the urine has thrown no light upon the source of the bleeding in such cases, and no example of the kind has come to an autopsy.

Pyuria.—When accidental admixture can be excluded, the presence of pus in the urine affords important evidence of a lesion in or in connection with the urinary tract.

The appearance of urine containing pus depends upon the quantity present and upon its reaction. From acid urine the pus tends to settle as a dense deposit of a yellowish or greenish hue, whereas the supernatant urine is clear. In alkaline urine the deposit is stringy and less circumscribed, and tends to cling to the sides of the containing vessel, whilst the urine remains turbid. Under the microscope very many leukocytes are seen, mostly degenerated, hyaline and globular, and often with highly refractive fat globules in their substance. Numerous epithelial cells of particular kinds, accompanying the leukocytes, may give an indication of the seat of the mischief. The time-honored teaching that pus in acid urine is usually of renal origin, whereas alkaline urine containing pus indicates a vesical lesion, often holds true, but the reaction of the urine is mainly dependent upon the nature of the infective organism at work in producing the pyuria, and whereas in cystitis due to *Bacillus coli* the urine tends to remain acid, the organisms of the *proteus* group may cause pyelitis by extension, and pyuria with alkaline urine.

The pus present in the urine may have its origin in a purulent urethritis, usually gonococcal, but sometimes due to other organisms. Cystitis is always accompanied by pyuria, which may be of any degree from the presence of a few leukocytes upward. Tuberculous disease of the kidneys is an important cause of pyuria, and in such cases the urine is acid, unless there be a mixed infection. Pyelitis by extension and calculous pyelitis are also attended with pyuria. In pyonephrosis the discharge of pus is apt to be intermittent, and when an abscess in a neighboring part opens into the urinary passages there is usually a copious discharge of pus for a time, followed by a more or less rapid cessation of the pyuria. Urines which contain pus are necessarily albuminous, but the presence of an amount of albumin out of all proportion to the pus offers a strong presumption of a renal origin.

Of the tests for pus in urine microscopic examination is the most conclusive. The ropy condition produced by the addition of a caustic alkali is often of value. When a layer of ozonic ether is poured upon the top of the urine in a test tube, and gently shaken with it, streams of oxygen bubbles rise through the ethereal layer if the urine contains pus; but as Dixon Mann points out this test fails to discriminate between true pyuria and the presence of mucus derived from the urinary mucous membranes.

When purulent urine is passed through a filter paper the pus left upon the filter yields a blue color with tincture of guaiacum, without any addition of ozonic ether or other oxidizing agent. In performing this test care should be taken that the filter paper used does not itself yield a blue color with the reagent.

Chyluria.—The passage of chylous urine indicates the opening of a lymphatic vessel into the urinary passages. This event is usually due to

the presence of the *Filaria sanguinis hominis*, but there are cases met with in patients who have never resided in a tropical climate, in whom the presence of chyluria cannot be ascribed to any parasitic cause.

The excretion of the chylous urine is usually intermittent, and is determined by such causes as the taking of food and the posture of the body. The fat which imparts the milky appearance is in extremely fine division, the minute particles being far smaller than the fat globules in fresh milk. The microscopic appearances are more nearly imitated by mixing condensed milk with water. That the opacity is due to fat may be shown by shaking the urine with ether. The fat dissolves in and is separated by the ether, whereas the subjacent urine is left clear or only slightly turbid.

Chylous urine sometimes sets into a jelly after it is passed, but after a short time liquefies once more. Occasionally the setting occurs in the urinary passages, with distressing results. Albumin and albuminoses also occur in chylous urines, and the presence of blood often imparts to it a pink tint. Under the microscope leukocytes and red blood corpuscles are seen, but no renal elements.

Fibrinuria.—In rare instances the urine has been observed to form jelly-like masses after it was passed, apart from the presence of chyluria. This phenomenon has sometimes been associated with grave forms of renal disease with highly albuminous urine. When hemorrhage occurs into the urinary passages fibrin is also, of necessity, excreted, and clots may form in the bladder or elsewhere.

Pneumaturia.—The passage of gas bubbles with the urine, which is sometimes attended with a clearly audible sound, may arise from two wholly different causes. In some cases the gas finds its way into the bladder from the lower intestine, passing through a fistulous opening which is usually a result of a malignant growth with ulceration. Passage of fæcal particles and debris per urethram will confirm the diagnosis of perforation. True pneumaturia, on the other hand, is a sign of infection of the bladder, and the liberation of large quantities of gas by bacterial action. If only a small quantity of gas be formed, it will be rapidly absorbed and will not pass as such.

In the great majority of cases the symptom is associated with diabetes, and the gas expelled is carbon dioxide, liberated by the fermentation of glucose within the urinary tract. However, this is not always the case, and Adrian and Hann have recently described as not very rare a class of case in which glycosuria is absent, and the gas is formed by the action of bacteria of the colon group or *Bacillus lactis aërogenes* upon proteins present in the urine of patients with cystitis.

ABNORMALITIES OF THE URINE DUE TO DISORDERS BEHIND THE KIDNEY.

Almost any disturbance of the metabolic processes of which the body is the seat will induce deviations from the normal in the urine. Some such deviations are very inconspicuous and not easy of detection, others are obvious and do not require to be looked for. Thus, the condition of the urine reflects, to some extent, the health or ill-health of the tissues at large.

Polyuria and Ischuria.—Some variations in the quantity of urine excreted may be classed as physiological, such as the increase due to copious drinking of liquids, and the decrease with profuse sweating; moreover, individual peculiarities play an important part in determining the volume of the urine or, more strictly speaking, the amount of liquid ingested.

The influence of diuretic drugs and beverages must be taken into account, and the profound influence of the nervous system, which reaches its limits in the polyuria of fright on the one hand, and hysterical anuria on the other. Among morbid conditions there call for special mention the ischuria of fevers and the polyuria which is a common symptom of convalescence from these, the polyuria which accompanies the absorption of dropsical effusions, the ischuria of diarrhœa, and the excessive polyuria of diabetes mellitus and diabetes insipidus. The influence of renal disease upon the quantity of urine is discussed elsewhere.

The Colors of the Urine.—The color of the urine is the most obvious of its characters, and the changes which it undergoes in disease have been recognized as of diagnostic value since the days of Hippocrates and Galen. For clinical purposes urines may be conveniently classed as: (1) Yellow and orange; (2) pink and red; (3) brown and black; and (4) green and blue. Abnormalities of tint may be due to changes in the relative amounts of the pigments which may be strictly classed as urinary, to the presence of body pigments which are not normally excreted by the kidneys, or to pigments derived from articles of food or drugs.

Yellow and Orange Urine.—The yellow tint of normal urine, which varies in depth with its concentration and with the amount of pigment excreted, is due to urochrome, for the other normal pigments are present in quantities so minute that they have no obvious coloring effect. There is little doubt that the amount of urochrome is materially affected by disease, but we have no exact knowledge of these variations, nor, indeed, of where this pigment is formed.

Urines rich in urobilin show the dark absorption band of that pigment, situated near the solar F line, and have a richer orange tint than normal urine. Whereas, urochrome retains its yellow tint on dilution so long as any color remains visible, very dilute solutions of urobilin have a pink hue, and when urine rich in this pigment is examined in a conical glass, a pinkish tint is visible at the apex of the cone. Uro-erythrin in solution imparts a fiery orange tint, which may even suggest the presence of blood, whereas urate sediments colored by it are pink in color. If a specimen of urine be acidified and shaken with amylic alcohol, the amylic extract will show the spectroscopic bands of urobilin, uro-erythrin, and hæmatoporphyrin if these pigments are present in more than minimal amounts.

Certain drugs modify the yellow color of urine. Chrysophanic acid, which is contained in rhubarb and senna, has this power, as also has santonin. In both instances the color of the urine is changed to pink by the addition of an alkali. A small admixture of bilirubin imparts a brownish-orange tint.

Pink and Red Urines.—The commonest cause of a pink or red color of urine is the presence of oxyhæmoglobin, but when the quantity of blood pigment is scanty it is usually changed to methæmoglobin and imparts a smoky tint.

In the condition known as hæmatoporphyrinuria, which will be discussed later, the color of the urine varies from that of port wine to absolute blackness, but the small amounts of hæmatoporphyrin which are present in various

morbid conditions, although they may greatly exceed the normal traces, do not appreciably modify the color of the urine. Rosanilin, when administered as a drug, renders the urine pink, and eosin, which is contained in certain varieties of sweetmeats, also imparts a pink color, which is accompanied by a brilliant green fluorescence. In the case of a boy who wished to simulate hæmaturia, and described symptoms suggestive of renal colic, the coloration of the urine was found to be produced by soaking in it a piece of Turkey-red cloth, which he carried in his pocket for the purpose. To alkaline urine chrysophanic acid may impart a deep pink color.

Brown and Black Urines.—Owing to statements by Hippocrates and Galen as to the peculiarly evil prognostic significance of black urine, these varieties have received much attention from medical writers, but in literature earlier than the commencement of the nineteenth century no distinction was drawn between urines which are black when passed and those which blacken on standing. Various causes may give rise to such peculiarities of coloration, and the conditions with which they are associated differ widely in gravity.

Urines rich in bile pigment, and especially those in which some biliverdin is present, often approach to blackness, and the same is true of some which contain blood or hæmoglobin. Methæmoglobin, even in small amounts, imparts a brown or smoky hue, and it is probable that many of the black urines of early writers belonged to this class. Some were almost certainly passed by patients with paroxysmal hæmoglobinuria, and the name of "black-water fever" bears witness to the production of blackness by altered hæmoglobin. In some cases of hæmatoporphyrinuria also the urine may fairly be described as black.

In some cases of indicanuria the urine darkens on standing, and becomes dark brown or even black. The color is not due to the indoxyl sulphates, which are colorless, but to higher oxidation products of indol. This variety of dark urine is not so well recognized as it should be, and it is probable that the condition in question has occasionally been mistaken for melanuria. When such urines are warmed with nitric acid, blackening results; and when Jaffe's test for indican is carried out, chloroform takes up abundance of purple pigment, indigo blue and red, whereas the supernatant liquid remains as black as before.

In true melanuria, indicative of widespread melanotic sarcoma, the urine is usually of normal color when passed, very seldom brown. On exposure to air it darkens from the surface downward, becoming first brown and later absolutely black.

The darkening of alkapton urines on exposure to air follows a very similar course, but the two conditions are easily distinguished by simple tests.

In the rare condition to which Virchow gave the name of ochronosis, in which the cartilages are as black as ink, dark urine, which blackens on standing, is sometimes passed for many years. The nature of this pigmentation is obscure. Osler has described surface staining such as accompanies ochronosis in some elderly alkaptonurics, in whom there was evidence of staining of the aural cartilages and conjunctivæ; but, on the other hand, it is certain that some ochronotic patients who pass dark urine are not alkaptonuric. In several of the recorded cases the development of ochronosis has followed the application of carbolic acid to ulcers over many years; but the nature of the black urine in a few cases remains obscure.

Some drugs cause the secretion of urine which blackens on exposure to

air; thus, carboluria is a familiar phenomenon, which is ascribed to the excretion of hydroquinine, and among other drugs which produce like effect may be mentioned naphthalene, salol, creosote, thallin, and, to a less degree, salicylates. The leaves of uva ursi contain arbutin, from which hydroquinone is formed, and this may cause a conspicuous darkening of the urine of patients taking that drug.

Green and Blue Urine.—Urines which contain bile pigment almost wholly in the form of biliverdin have a deep green color, but with this exception it may be stated that practically all green urines, as well as those which have a blue color, owe their tints to methylene blue, Anyone familiar with the reactions of such urines can easily convince himself of the nature of the coloration, but it is not always easy to ascertain how the methylene blue was introduced into the alimentary canal. Sometimes it has been administered as a drug, and the cause of the phenomenon is obvious; sometimes it has been taken in sweetmeats, and it should be mentioned that some white sweets contain it. Sometimes, again, one is driven to the conclusion that a pill of methylene blue has been introduced accidentally or otherwise among those of a different kind which the patient is taking. This much is certain, that until coloration by methylene blue can be definitely excluded, speculation as to the nature of a green or blue urine is wasted.

From urines tinted by methylene blue the abnormal pigment is for the most part removed by simple filtration, even though the urine appears perfectly limpid. The blue sediment may be dissolved off the filter with chloroform, when the blue solution shows a characteristic absorption spectrum. When the chloroform solution is shaken with an alkali the blue is replaced by a pink tint.

A surface scum of indigo blue is sometimes formed upon the surface of alkaline urines by the spontaneous decomposition of indoxyl-glycuronic acid, and many years ago when indigo blue was extensively employed as a drug in the treatment of epilepsy, remarkable coloration of the urine was observed. However, it may be confidently stated that clear urines rendered green by indigo blue are not met with.

On the other hand, it must be acknowledged that a few records of green urines, which can hardly have owed their tint to biliverdin, were recorded before the discovery of methylene blue, as in the case of a boy, recorded by Bull, in which the bark of *Cytisus alpinus* had been chewed.

Hæmatoporphyrinuria.—Among conditions which are characterized by abnormal pigmentation of the urine, this calls for special mention. It usually results as one of a group of toxic symptoms from the taking of sulphonal, much more rarely of trional, over long periods. Hæmatoporphyrinuria may develop after a few doses of the drug, or only after it has been taken for several years in uniform nightly doses. It may even appear some days after the drug has been discontinued. Under any of these circumstances its prognostic significance is grave.

It is a remarkable fact that whereas the group of symptoms of which hæmatoporphyrinuria is one have been observed in a large number of female patients, it has very seldom been seen in males. It will be well to limit the application of the term to cases in which the urine assumes a deep red color like that of port wine, or is even nearly black, and is found to contain quantities of hæmatoporphyrin which are far in excess of those usually present in urine. Normal urines contain minute traces of hæma-

toporphyrin, in a variety of morbid conditions, and especially in chronic lead poisoning the normal traces are considerably exceeded; but the tint of the urine is not materially altered thereby. In cases of hæmatoporphyrinuria, in the restricted sense, the dark color of the urine is not due to the pigment in question, but, as Hammarsten first pointed out, to other abnormal pigments which accompany it, of which little is yet known. The color of such urine cannot be simulated by the addition of hæmatoporphyrin, and when this pigment can be separated from the dark urines their color is not materially affected by its removal.

The absorption spectra of hæmatoporphyrin are complex and very characteristic, and the bands are dark and sharply defined. Yet in these urines its detection by means of the spectroscope is by no means so easy as might be expected. The pigment often existing in them is the so-called "metallic" form, that is to say, in a combination in which it shows two bands which closely resemble those of oxyhæmoglobin.

The quantity present varies greatly, and it is sometimes necessary to precipitate the pigment before a certain diagnosis can be made. This may be done by the addition of calcium chloride and lime water, Salkowski's method. The precipitate, which carries down all the abnormal pigments, is extracted with alcohol to which sulphuric acid has been added, and the acid alcoholic extract will show the spectrum of acid hæmatoporphyrin.

Hæmatoporphyrinuria may be suspected when urine is excreted which resembles port wine in color, which shows absorption bands resembling those of hæmoglobin, but contains no albumin and does not give the guaiacum test for blood. Sometimes the mere addition of an acid brings out the characteristic spectrum of acid hæmatoporphyrin. If the patient has recently taken sulphonal the condition is at once explained. The drug should be stopped, and sodium bicarbonate should be given in large doses, a plan of treatment which has proven efficacious in not a few cases.

Very rarely hæmatoporphyrinuria has been met with apart from the administration of sulphonal or its allies. Under such circumstances the symptom is of no such evil omen, and there is no special liability of the female sex. The symptom may persist for years, may recur at intervals, or may assume a paroxysmal form resembling paroxysmal hæmoglobinuria, as in a case recorded by Pal. In some cases the urinary anomaly has recurred in association with annual attacks of *hydroa æstivale*.

Blood counts, made at intervals during and after attacks of hæmatoporphyrinuria, afford evidence which is sufficiently conclusive that the phenomenon is not a sign of an excessive hæmolysis, but is due to a derangement of hæmoglobin catabolism, a large part of the hæmoglobin following the path which leads to the excretion of traces of hæmatoporphyrin even in health.

Urobilinuria.—Urobilin, which is recognized in urine by its dark absorption band near the solar F line, is mostly excreted in the form of a chromogen, which becomes converted into the pigment after it is excreted. Urobilin is mainly formed by the action of the intestinal bacteria upon bilirubin, and the bulk at least of the urobilin of urine is absorbed from the alimentary canal—whether there is not another source of the pigment within the body is a question which is not yet finally settled. The conditions which bring about an increased excretion of the pigment or its chromogen in the urine are multiple, and this deprives its presence of much of the clinical significance which it would otherwise possess. Mere consti-

pation may lead to urobilinuria. Excessive hæmolysis of moderate degree, with consequent pleochromia of the bile, is a well-recognized cause, and urobilinuria is to be expected in cases of pernicious anæmia.

The influence of the liver upon the excretion of urobilin is beyond question, and urobilinuria is common in association with hepatic disease, an association the nature of which is difficult of explanation. After an attack of obstructive jaundice, while the skin is still yellow, although bile is again entering the intestine, the bile pigment tends to be replaced in the urine by a copious excretion of urobilin, and the term urobilin jaundice has been frequently employed. It should be mentioned, however, that there is no evidence that pigmentation of the skin and other tissues is ever due to the presence in them of urobilin in place of the unaltered bile pigment.

In some cases an excessive urobilinuria has been observed by Rolleston and others as a result of the taking of trional, and in fevers of various kinds the urine frequently shows a strong urobilin band.

Uro-erythrinuria.—The frequency of pink urate sediments bears witness to the frequent presence of uroerythrin in the urine in considerable quantities. This very unstable pigment has a great power of coloration. Of the material from which it is formed and of its place in the classification of pigments, nothing is yet known. It is probably not a constituent of strictly normal urines, but even a slight digestive disturbance may cause it to appear. In fevers it is commonly met with, but all the clinical evidence available connects its presence in the urine with functional derangements or organic disease of the liver. Patients whose urine deposits uratic sediments of a deep pink color almost invariably have some hepatic trouble which is manifested by other signs, whether it takes the form of cirrhosis or of malignant tumors, or of the nutmeg change which results from circulatory derangements with backward pressure and chronic congestion. When no uratic sediment falls, the pigment, if abundant, imparts to the urine a fiery orange color, which is changed to a dirty greenish tint by the addition of an alkali.

Indicanuria.—Indoxyl is met with in urine mainly in combination with sulphuric acid, as the so-called urinary indican—a substance which is wholly different in nature from the indican of plants, which is a glucoside. A small fraction is in combination with glycuronic acid, and it is probably as the result of the spontaneous decomposition of indoxyl-glycuronates that deposits of free indigo blue are sometimes formed in alkaline urines.

Even in health the protective mechanisms which lead to the formation of such compounds, and so render the indoxyl harmless, are called into play to a small extent, and indoxyl-sulphates contribute to the normal quotum of aromatic sulphates. The parent substances of the urinary indican are the proteins of the food, which are in part decomposed in the intestine by the bacteria so abundantly present there. The particular portion of the protein molecule from which the indol is derived is the tryptophane fraction.

In many morbid conditions, and in some which can hardly be called morbid, such as simple constipation, the formation of indol in the intestine and the excretion of indoxyl compounds in the urine is conspicuously increased, and such increase may be interpreted as a measure of bacterial decomposition in the alimentary canal. That in the great majority of cases the increased excretion has this significance seems certain, although we cannot be sure that some of the indol formed does not undergo further changes in the tissues, so that the excretion of indigo precursors does not necessarily afford

an accurate measure of the process. Indicanuria has sometimes been observed in cases in which the cavities of the body contained fœtid pus, as, for example, in cases of fœtid empyema, and such collections may afford other sources of indol.

In a case of fœtid empyema which was recently under the observation of the writer, in which the pus contained *Bacillus coli* as well as the pneumococcus, there was a conspicuous increase of urinary indican, but this disappeared when the bowels were freely evacuated after a dose of castor oil, and was probably of intestinal origin.

In many instances urines rich in indoxyl sulphate are normal in appearance, but sometimes they have a brown tint which is greatly intensified by exposure to air, or by the addition of oxidizing agents. In cases in which urine having such characters is passed, care should always be taken to exclude this cause, for it is highly probable that the condition has before now been not unfrequently mistaken for melanuria. The application of the ordinary tests will reveal the presence of large quantities of indican, but the color of the urine was ascribed by Baumann to higher oxidation products of indol, seeing that the indoxyl sulphates are colorless compounds.

When urines containing indican are boiled with hydrochloric acid, to which a trace of nitric acid or of bleaching powder solution has been added, they undergo conspicuous darkening, and indigo pigments are formed. If hydrochloric acid be alone used indigo red is formed in excess; the oxidizing agents favor the formation of indigo blue. If they be added in too large quantities, isatin is formed and the result of the test may be deceptive.

If, after cooling, the acid liquid be shaken with chloroform, the chloroform acquires a deep purple color, from admixture of the red and blue pigments, and with the spectroscope the absorption band in red, due to indigo blue, may be observed. If the chloroform be evaporated the two pigments may be separated by washing the residue with alcohol which takes up the indigo red, whereas the indigo blue which remains undissolved forms a blue solution in chloroform.

Melanuria.—The excretion of melanin, or rather of its chromogen melanogen, in the urine is a sign of great diagnostic value, as indicating the presence of a disseminated melanotic growth. In cases in which the tumor is still limited to its primary seat no melanuria is observed. Only when secondary tumors are forming is melanogen excreted, and the occurrence and intensity of the melanuria appear to be chiefly determined by the invasion of the liver.

It is often stated that melanuria occurs apart from melanotic tumors, but, although such occurrence cannot be wholly excluded, it must be exceedingly rare. The cases usually quoted in support of this contention are not wholly convincing. Some were recorded before the most characteristic reactions of melanin were known, and some at least were in all probability examples of indicanuria in which the urine darkened on standing. Nevertheless, the diagnosis of melanotic growths seldom rests on melanuria alone, for the history of a primary melanotic growth of the eye or skin is usually forthcoming.

The urine has usually the normal color when fresh but quickly darkens on exposure to air and ultimately becomes black. Occasionally it has a brown color when passed. The addition of nitric acid in the cold causes immediate blackening, as also does that of a solution of ferric chloride.

This latter reaction is the most satisfactory of all, for it is not obtained in any of the other conditions which simulate melanuria more or less closely. Unless it is obtained melanuria should never be diagnosed, but in the early stages, whilst the amount of melanogen excreted is small, the blackening may only be partial. Bromine water produces a yellow or chocolate-colored precipitate, which rapidly blackens (Zeller's test). Von Jaksch has also pointed out that the urine in melanuria yields a deep Prussian-blue color when sodium nitroprusside and potassium hydrate are first added and acetic acid is afterward added in excess. However, this test is yielded by other than melanin urines, and even in the cases under discussion is not to be attributed to melanogen.

Lithuria.—Recent years have brought about a great change in our conceptions as to the origin of uric acid in the economy, and the significance of variations in the amounts excreted in the urine. It has been recognized that it is the end product of a special line of catabolism of substances which contain the purin nucleus, the nucleoproteids of the food and tissues. This path runs parallel to, but distinct from, that by which the ordinary amino-acid fractions of proteins are broken down to urea; but it is probable that some of the uric acid is itself destroyed and yields a portion of the urea excreted. The fairly uniform ratio of the excretion of uric acid to that of urea in health is due to the similar uniformity of the relative quantities of albumins and nuclein broken down. It is, however, probable that, even in man, the synthetic processes which must take part in the formation of the relatively immense output of uric acid by birds and reptiles are not wholly in abeyance. The uric acid of urine is in part exogenous and derived from the purins of the food, and in part endogenous, derived from the nucleoproteids of the tissues. Even this latter fraction differs somewhat widely in amount in different individuals.

The deposition of amorphous sediments of urates as the urine cools is a very common event, and it cannot be too strongly insisted that this must not be interpreted as a sign that the daily output of uric acid is in any way above the normal limits. It often results from mere concentration of the individual specimen, due to excessive loss of water by the skin, as after violent exercise. Various factors contribute to the formation of such sediments, such as the degree of acidity of the urine, and an excessive output is one of these contributory factors. Even the temperature of the air has a potent effect, and uratic deposits are therefore more often seen in winter than in summer. Clinically, uratic deposits are common in the urine of patients with fevers and of sufferers from gout and various liver diseases. Their color varies from a pale yellow tint, due to included urochrome, to a deep pink, due to combined uro-erythrin.

This clinical association with gout has no relation to the excess of uric acid in the blood. The many laborious investigations which have been carried out of recent years upon the urine of the gouty have failed to show any constant excess or decrease of the uric acid beyond the somewhat wide normal limits. Only just before the acute attack of gout has a diminished excretion been demonstrated, followed by an excessive output as the attack subsides.

A diet rich in purin substances, as in thymus feeding, causes a conspicuous increase of the excreted uric acid, and of morbid conditions the most obvious increase occurs in leukæmia, and is here attributed to the nuclein of the

broken-down leukocytes. Even sufferers from chronic gout excrete more uric acid when fed with thymus, but the increase is proportionately less than in normal subjects. Nor is the deposition of crystalline uric acid necessarily due to excessive excretion. In leukæmia it sometimes results from this cause, but many other factors are concerned, such as the degree of acidity, the proportions of salts and other constituents in solution, and, as Klemperer has shown, the amount of urochrome present. This observer finds that deficiency of urochrome has an important influence in favoring the deposition of uric acid.

Here, again, apart from any excessive excretion of uric acid, there is a clinical association often observed between the deposition of uric acid sand, the formation of uric acid calculi, and the familiar phenomena of gout. What is the nature of this association is not yet clearly understood.

In addition to uric acid the urine contains smaller quantities of the closely allied purin bases, xanthin, hypoxanthin, etc. These bases also are partly of exogenous and partly of endogenous origin; being more soluble, they play little known part in pathology, but in very rare cases calculi consisting of xanthin have been formed in the kidneys or urinary passages.

No idea of the amount of purin substances excreted can be obtained save by exact quantitative estimation of the daily totals. The estimation of uric acid can now be carried out without any special difficulty by Hopkins' method, while the purinometer of Walker Hall allows an estimate to be formed of the total purin output, both uric and xanthin bases, by a method so simple that it is available for clinical purposes.

In conclusion, it may be mentioned that kidneys damaged by disease appear to exercise a less pronounced retentive effect upon the comparatively insoluble uric acid than upon the very soluble urea.

Kreatinin Excretion.—Kreatinin derived from the kreatin of muscle is partly an exogenous and partly an endogenous urinary constituent, to the amount of about 1 gram per diem. The exogenous excretion is derived from the meat taken as food. The endogenous excretion, which may be estimated by placing the patient on a kreatinin-free diet, has been found to be increased during acute fevers, and, indeed, in any condition which is accompanied by an excessive breaking down of the muscular tissues. In cases with conspicuous splenic enlargement Macleod has found the endogenous kreatinin much diminished, and in diseases in which chronic atrophy of muscles is a feature, such as progressive muscular atrophy and the myopathies, a diminished output is also observed, the total bulk of muscle tissue being in such cases much below the normal.

Phosphaturia.—The term phosphaturia as commonly applied is a misnomer, seeing that the deposition of amorphous phosphates in the urine is no indication of an abnormally great excretion of phosphoric acid, but merely of the abolition of its normally acid reaction. Such deposition occurs when the urine undergoes ammoniacal decomposition, but the cases in which this occurs are not spoken of as examples of phosphaturia.

Alkalinity from fixed alkalies may be brought about in various ways, and its inevitable result is a separation of the earthy phosphates. Often it is a physiological event, and results from such simple causes as the taking of a diet rich in vegetables, or the drinking of alkaline mineral waters. Again, during the so-called "alkaline tide" which sets in some hours after a meal, the urine may become amphoteric or alkaline, not by the addition

of alkali, but by the withdrawal of acid in the secretion of the gastric juice. A like result may follow copious vomiting or lavage of the stomach.

The excretion of alkaline urine as the result of none of these causes occurs as a definite pathological event, which is often associated with neurasthenic symptoms, and is apt to assume in the minds of the patients a gravity out of all proportion to its real importance. In a considerable class of cases such phosphaturia is associated with disorders of the sexual organs. The pathology of many of these cases is very obscure.

In a certain class of case, which is especially common among children, the urinary anomaly is due to an excessive output of calcium in the urine. The excess of calcium combines with the phosphoric acid and causes a relative increase of insoluble basic phosphates and a relative decrease of the soluble acid phosphates to which the acidity of the urine is due.

It is a well-known fact that in health the bulk of the calcium is excreted by way of the colon, and only a relatively small amount in the urine. Soetbeer, who has made a special study of the condition under consideration, whose results have been confirmed by Tobler and other observers, found that in association with the increase of calcium in the urine there is in these cases a diminution of its intestinal excretion. Soetbeer, therefore, places the seat of the morbid process in the mucous membrane of the colon, a species of colitis. It must not be supposed, however, that all cases of phosphaturia in children are of this nature.

In cases of phosphaturia with increase of urinary calcium, a regulation of diet, with substitution of food poor in calcium for those rich in salts of that metal, is indicated. In cases with nervous disturbances general tonic treatment usually proves the most useful. The administration of acids, with a view to increasing the urinary acidity, is very uncertain in its effects; but R. Hutchison has shown that acid sodium phosphate is more effectual than mineral acids, a result which agrees with what might be expected on theoretical grounds, viz., that an increase of phosphoric acid in the urine would rather tend to manifest itself by an increase of the acidity than by the production of the phenomenon commonly spoken of as phosphaturia.

Oxaluria.—From the clinical standpoint, the importance of calcium oxalate as a urinary constituent is due to its sparing solubility and the frequency with which it is deposited in crystalline form, or even appears as concretions in the kidneys or bladder. Such deposition of calcium oxalate depends upon the interaction of a variety of causes, of which excessive excretion is only one, although by no means an unimportant one.

Of the small daily output of oxalic acid in human urine, which, under normal conditions, does not exceed 1 or 2 mg., part is exogenous and derived from vegetable foods, and part is endogenous. Even upon an oxalate free diet, such as pure milk, as also during abstinence from food, some oxalate continues to be excreted. Only a portion of the oxalate of the food finds its way in the urine; some is apparently decomposed in the alimentary canal rather than broken up in the tissues, seeing that injected soluble oxalates are excreted quantitatively. The administration of hydrochloric acid has been shown to promote the absorption of calcium oxalate from the food and to increase the urinary output; and it is probable that in the cases described by Begbie and others as examples of an oxalic acid diathesis, attended with neurasthenic symptoms, the deposition of oxalate crystals in the urine was, as Dunlop suggested, largely due to such increased absorption

as the result of the acid dyspepsia which was a prominent phenomenon of the condition.

In the older literature of the subject no clear distinction was drawn between the formation of crystals of calcium oxalate and an actual excessive excretion. Wide variations in daily output undoubtedly occur, some of which are due to the taking of vegetable foods rich in oxalate, such as rhubarb and spinach, as in the cases in which rhubarb freely eaten causes hæmaturia and the urine deposits crystals of calcium oxalate in great abundance. Increased excretion of oxalic acid has also been observed in a variety of different diseases, and especially in connection with jaundice and with diabetes; but in no disease is such excessive excretion found to be constant, nor is there any sufficient evidence of the occurrence of a metabolic error as the result of which an increased output of endogenous oxalate, as distinguished from the deposition of crystals, persists over long periods. The origin of the endogenous oxalic acid is still very obscure—some of it is probably of protein origin, some may be derived from purins, and it has been shown by Lommel that the administration of gelatin by the mouth is followed by an increased oxalate excretion; this suggests the gelatin of the tissues as one at least of its probable sources.

In the present state of our knowledge, attempts to combat the tendency to deposit calcium oxalate from the urine may be directed along two separate lines. In the first place we may limit the output by eliminating as far as possible from the diet articles containing oxalic acid. Many vegetables come into this category, and especially rhubarb, spinach, and tea, and on the basis of Lommel's observation gelatin should also be excluded. In the second place we may seek to produce the conditions best calculated to further the holding of calcium oxalate in solution. The acidity of the urine may be augmented by a meat diet, and following the lines suggested by Klemperer and Tritchler, we may endeavor to diminish the calcium of the urine, and at the same time to increase the amount of magnesium present. The authors quoted have shown that whereas excess of calcium salts tends to further precipitation, excess of salts of magnesium tends to inhibit it. This object may be attained by the avoidance of foods rich in calcium, such as milk, eggs, etc., and the prescription of vegetable foods comparatively rich in magnesium, such as rice, farinaceous foods, peas, beans, and coffee.

Leucin and Tyrosin in Urine.—The excretion of these amino-acids in the urine was first observed by Frerichs in a case of acute yellow atrophy of the liver, and it is with this disease that their excretion is especially associated, and acquires considerable diagnostic importance. In cases of phosphorus poisoning also they are sometimes met with, but much less frequently, and as a rule in smaller quantities.

In cirrhosis of the liver they have been sought for in vain, but Dixon Mann has recently described their presence in the urine in some cases of nutmeg liver resulting from cardiac disease. In pernicious anæmia they have occasionally been found by Laache and von Noorden. That these protein fractions are sometimes excreted unchanged by cystinurics is an undoubted fact. Tyrosin is occasionally deposited from urines containing it as a sediment of delicate acicular crystals grouped into sheaves, whereas leucin is hardly ever thrown down spontaneously. Usually the crystallization of both substances occurs only after the urine has been con-

centrated, and when their presence is suspected the urine of twenty-four hours should be precipitated with lead acetate and filtered. After the excess of lead has been removed by a stream of sulphuretted hydrogen, and the lead sulphide filtered off, the filtrate is evaporated down to a syrup. From the residue the bulk of the urea may be removed by treatment with cold absolute alcohol, and what remains is extracted by boiling it with dilute ammoniacal alcohol. The filtered extract is once more evaporated to a small bulk and allowed to stand. Needles of tyrosin and greenish spherules of leucin may then be deposited. Care must be taken not to mistake spherules of ammonium urate for leucin.

To insure certainty special tests for leucin and tyrosin should be employed, and Millon's test should at any rate be tried. All urines yield some pink color when heated with Millon's reagent, even in the cold. When much tyrosin is present the reaction is very intense on warming. When the urine gives no more coloration than does a control of normal urine the presence of any considerable quantity of tyrosin may be excluded.

Until recently it was generally supposed that the grave destruction of the parenchyma of the liver, in the diseases in which leucin and tyrosin are excreted, arrested the formation of urea from these and other protein fractions, and the greatly diminished output of urea in many cases of yellow atrophy was adduced as an argument in favor of this view. However, Richter has shown that these substances may be found in the urine in cases of acute yellow atrophy in which urea formation is little impaired, and many now hold that when the urea is diminished it is rather because the antecedent ammonia is utilized to neutralize acids which are being formed in excess.

Since Jacoby showed that in aseptic autolysis of the liver leucin and tyrosin are abundantly formed by the action of the enzymes upon the proteins of the organ, the view has gained acceptance that their excretion is a result of an autolysis intra vitam, and receives support from the fact that in acute yellow atrophy these amino-acids are present in quantity in the liver, as well as in the blood and urine. On the other hand, Neuberg and Richter suggest that the destruction of the hepatic parenchyma, which certainly occurs, does not suffice as the source of such amounts of leucin and tyrosin as are sometimes to be found in the blood.

It seems probable that the occasional excretion of leucin and tyrosin in cystinuria is due to a wholly different cause from that observed in liver disease, and is part of a widespread failure to deal with protein fractions.

Alkaptonuria.—This is a very rare urinary anomaly, of which some 40 or 50 cases are on record. Alkapton urine darkens on exposure to air, passing through shades of brown to absolute blackness. The darkening, which is accompanied by absorption of oxygen, is greatly hastened by the addition of an alkali. When the urine is heated with Fehling's solution, a deep brown color develops and a copious reduction occurs. An ammoniacal solution of silver nitrate is quickly reduced by it in the cold. When it is heated with Nylander's solution a darkening occurs, due to the action of the alkaline reagent upon the urine, but no black precipitate forms from reduction of bismuth salt. When a *dilute* solution of ferric chloride is added to the urine drop by drop a deep blue color appears for a moment as each drop falls, until oxidation is complete.

The condition is usually detected during infancy by the staining of napkins as by photographic reagents, or in later life in consequence of the

reducing action. In not a few instances it has been brought to light on application for life insurance.

Alkaptonuria is not a disease, but rather a "sport" of metabolism or chemical malformation. It is congenital, lifelong, and harmless, and apt to occur in families, not a few of which are the offspring of consanguineous marriages. It is rarely directly inherited. The error consists in a failure to complete the catabolism of the aromatic fractions of proteins, tyrosin. and phenyl-alanin, and the peculiar properties of the urine are due to the presence in it of an aromatic acid derived from these, homogentisic or hydroquinone-acetic acid. The statement that a second aromatic acid, uroleucic, is also present in some cases rests upon a misapprehension.

The tyrosin and phenyl-alanin of both the food and tissue proteins are concerned. During abstinence the output of homogentisic acid is diminished, but is not arrested. A diet rich in proteins greatly increases the output, and when tyrosin or phenyl-alanin is given by the mouth to an alkaptonuric an almost corresponding quantity of homogentisic acid is added to the output; whereas these amino-acids when taken by normal persons are destroyed and their benzene ring is broken up. The error is not one of varying degree. The quantities of homogentisic acid excreted by different alkaptonurics are singularly uniform when the nature of the diet and the ages of the patients are allowed for, and there is reason to believe that the error is in all instances complete and maximal in degree.

From a clinical standpoint the importance of alkaptonuria is slight. A knowledge of the properties of the urine will allow a reassuring prognosis to be given. Inconvenience may be caused by the staining of clothing or by the inability to effect a life insurance, owing to the reducing action of the urine. Some dysuria has occasionally been present, and some elderly alkaptonurics mentioned by Osler have exhibited surface pigmentation such as is associated with the rare condition described by Virchow under the name of ochronosis, in which the cartilages acquire an inky blackness. The association of ochronosis with alkaptonuria has recently been demonstrated postmortem by Wagner and by Gross and Allard.

In a very few instances a condition of the urine indistinguishable from that met with in congenital alkaptonuria has been temporarily observed, and Falta and Langstein have shown that some patients with grave diabetes have less power of destroying homogentisic acid given by the mouth than have healthy people.

To the physiologist and chemical pathologist the interest of alkaptonuria is very great, for the abundant study which has been devoted to it of recent years has thrown most valuable light upon the metabolic processes concerned.

Cystinuria.—The excretion of cystin in the urine is of considerable clinical importance, because this sparingly soluble substance is readily deposited, and cystinurics are very liable to develop renal or vesical calculi and to suffer from cystitis. The condition, which is rather less rare than alkaptonuria, is recognized by the formation of a sediment of very characteristic colorless hexagonal crystals, soluble in ammonia and in hydrochloric acid. Scarcely tinted crystals of uric acid sometimes assume a somewhat similar shape, and starch granules have been mistaken for those of cystin and crystals of iodoform. If some of the sediment be dried upon a slide and some strong hydrochloric acid be allowed to flow over the crystals

beneath a coverglass, whilst the changes are watched through the microscope, beautiful prismatic crystals of cystin-hydrochlorate are seen to grow out rapidly from each hexagonal crystal, and to form a rosette which melts away as rapidly as it was formed, on the addition of a drop of water.

The quantity of cystin excreted is about 0.5 gram per diem, and in most instances the excretion persists for years and probably for life. In some cases the cystin has been known to disappear from the urine for a time, or may even have been only temporarily present. Cystin is said to be present in the sweat of cystinurics; in the fæces it is absent. No impairment of health results from the metabolic derangement as such, but the secondary results of its deposition in the urinary passages are often serious. In the case of an infant member of a cystinuric family Abderhalden found abundant deposits of crystalline cystin in the internal organs after death. Cystinuria is strongly hereditary, and has been traced through three generations. Sometimes it occurs in several children of parents who do not exhibit the anomaly.

It was shown by Baumann and Udranszky that some cystinurics excreted the diamines cadaverin and putrescin in their urine and fæces, and their observation has since been repeatedly verified. However, in a number of recent cases they have not been found, and in others they have only been present at intervals, on isolated days or on several successive days. In the fæces they have been comparatively seldom found. Cadaverin is much more frequently present than putrescin, but the two may occur in association.

Still more rarely leucin and tyrosin have been found, and their abundant presence in the urine was established beyond possibility of doubt in a case observed by Abderhalden and Schittenhelm. Cystin, leucin, and tyrosin are all primary fractions of proteins; cadaverin is easily derived from lysin and putrescin from arginin, and the view is now prevalent that cystinuria is a congenital error of protein metabolism, which is of different extent in different cases. In some cases the cystin fraction appears to be alone implicated, in others lysin, arginin, tyrosin, or leucin, and probably other amino-acids also. In one case recorded by A. Loewy and C. Neuberg, although cystin was the only protein-fraction excreted, administration of lysin by the mouth caused excretion of cadaverin, that of arginin the appearance of putrescin in the urine, whereas tyrosin and aspartic acid, when taken, were excreted as such. This case is up to now unique, and in several other cases no such effects have followed the administration of the several amino-acids.

The study of the metabolic peculiarities of cystinurics has yielded results which are very difficult of explanation, and the more the problem is investigated the more remote seem to be the chances of its satisfactory elucidation. Thus, in every case tested, except that of Loewy and Neuberg, in which cystin has been given by the mouth it has been completely destroyed, although the patients were all the time excreting cystin as such.

PROTEINS IN URINE OTHER THAN THE NORMAL PROTEINS OF SERUM.

When a protein foreign to the blood plasma is present in it, in any but very small quantities, it is got rid of by excretion by the kidneys. Hence the presence of such proteins in the urine has a wholly different significance from albuminuria, and in no way implies damage to the renal structures. Small

quantities of foreign proteins, on the other hand, may continue to circulate in the blood until disposed of in other ways.

Hæmoglobinuria.—When hæmolysis of moderate degree is in progress, as in pernicious anæmia, the liberated blood pigment becomes converted into bile pigment, and the only effect upon the pigmentation of the urine is due to the presence of excess of urobilin, formed by the action upon the bilirubin of intestinal bacteria. When, however, a great and rapid hæmolysis occurs from any cause unchanged blood pigment is excreted by the kidneys and hæmoglobinuria results. Hæmolysis of the necessary degree may be brought about by a variety of different causes. It is a well-recognized fact that transfusion of foreign blood, *i. e.*, of the blood of an animal of different species, is followed by hæmoglobinuria, and one may suppose that the corpuscles which are broken down are those of the foreign blood. A number of poisons exert powerful hæmolytic actions, and of these potassium chlorate is the most important. Arseniuretted hydrogen and toluene-diamine also call for mention.

Bacterial poisons of various kinds have like effects, as witness the hæmoglobinuria which sometimes occurs in fevers. To this group probably belongs the hæmoglobinuria of newborn children which was first described by Winckler. The hæmolytic action of malarial parasites is well known, and in the variety of malaria known as black-water fever hæmoglobinuria is a prominent symptom, although it is believed by not a few that large doses of quinine contribute to the production of the effect in question. Hæmoglobinuria may also follow extensive burns, and is sometimes seen in athletes and others after violent muscular exertion.

The most remarkable of all the varieties is that known as paroxysmal hæmoglobinuria, the pathology of which is still very obscure. In some cases this malady would appear to have a syphilitic origin and in others a malarial, but not unfrequently no such antecedent cause can be traced. The exciting cause of the individual paroxysm is, in the great majority of cases, exposure to cold, and this connection is so obvious that it may be predicted with certainty that an adequate exposure will precipitate an attack. In a few other cases muscular exertion or traumatism figures as the exciting cause.

In association with a paroxysm of hæmoglobinuria some of the symptoms of peripheral asphyxia are almost invariably present, and in some cases the symptoms of Raynaud's disease are very pronounced. However, the association is a somewhat one-sided one, for in the majority of cases of Raynaud's disease, even of an extreme degree, hæmoglobinuria does not occur. The symptoms develop shortly after the exciting exposure to cold, and after-persisting for a few hours gradually pass away, leaving the patient apparently well until the next exposure. Although attended by little or no danger to life, paroxysmal hæmoglobinuria is little susceptible to treatment, save by protection from cold. In some cases antisyphilitic treatment has appeared to work a cure, and in some quinine has been found beneficial.

Some recent researches of J. Eason and of Donath and Langsteiner have thrown important light upon the nature of the processes at work in the production of paroxysmal hæmoglobinuria, although the nature of the toxic agent has not yet been made out. It has been shown that when blood withdrawn from a patient between the paroxysms is treated with a solution of potassium oxalate in normal saline no hæmolysis is produced by cooling in ice-cold water for half an hour, but that when the cooled blood is transferred

to an incubator at body temperature hæmolysis occurs. The corpuscles removed after cooling, and washed with and suspended in normal saline, do not undergo hæmolysis in the incubator, as they do when they are left in contact with the serum. When blood is removed during the paroxysm, and the corpuscles are at once separated and washed, they undergo hæmolysis when suspended in normal serum and placed in the incubator. Again the serum removed during the paroxysm has the power of destroying normal corpuscles, when the mixture is first cooled and then placed in the incubator, whereas the serum which has been previously chilled with its own corpuscles no longer possesses this power.

These results, and others obtained, are best explained by supposing that, to use Ehrlich's terminology, in the organism of a patient who suffers from paroxysmal hæmoglobinuria there is present a potential hæmolytic toxin which only becomes active under certain favoring conditions, the chief of which is exposure of the blood to a lowered temperature. This toxin is of dual nature, one part acting as amboceptor and the other as complement. It would seem then that the amboceptor which is the specific poison is constantly present in the blood of the patient and is not merely produced at the time of exposure, but that only when the temperature of the blood is lowered is it able to become attached to the red corpuscles of the cooled peripheral blood. When the blood regains the normal body temperature hæmolysis results under the influence of the complement, which is present in normal serum and is not peculiar to the disease under consideration. Only those corpuscles will be destroyed which, during the period of exposure to cold, have become linked with the amboceptor.

In appearance the urine of hæmoglobinuria varies greatly. In the slighter degrees, such as are sometimes met with in fevers, it may be pink and transparent, and may show the spectroscopic bands of oxyhæmoglobin with great distinctness. In cases of poisoning by potassium chlorate the pigment set free is wholly or almost wholly in the form of methæmoglobin. In paroxysmal hæmoglobinuria the urine has a deep red or brown color, approaching to blackness, and usually deposits a sediment of hæmoglobin—debris of a chocolate color. On spectroscopic examination the absorption band, in the red, of methæmoglobin is usually well seen, as well as the bands of oxyhæmoglobin.

In all cases the diagnostic feature of hæmoglobinuria, as distinguished from hæmaturia, is the absence of red corpuscles in the sediment. The particles of brownish debris are often seen to be grouped into cast-like forms. The presence of methæmoglobin in the urine is in no way peculiar to hæmoglobinuria, for the smoky urine of hæmaturia also contains the blood pigment in this form. In paroxysmal hæmoglobinuria some albumin may persist in the urine for a time after the blood pigment has ceased to be excreted, and abnormal amounts of urobilin and of hæmatoporphyrin are sometimes to be detected after the paroxysm.

The Bence-Jones Protein.—The excretion of this peculiar protein substance, which was first described by Bence-Jones in 1848, is one of the most remarkable of urinary anomalies. It is an albuminous substance which is not known to be formed in the organism under normal conditions; and as a constituent foreign to the blood it is readily excreted even by intact kidneys, and often in large quantities, up to as much as 70 grams in the twenty-four hours. Although rare, the phenomenon is of great diagnostic

importance, seeing that it may be the earliest recognized sign of an affection of the bone marrow known as multiple myeloma. Apart from disease of the bone marrow it has not been met with, and it is probable that the cases of supposed osteomalacia in which it has occurred were in reality examples of multiple myeloma.

The Bence-Jones protein has been found in the blood as well as in the urine of patients who have excreted it, but in the diseased bone marrow it has only been detected in small amounts. When once it appears the excretion is usually continuous until death ensues, but in some instances it has been intermittent. The quantity in the urine varies widely in different cases. The knowledge gained from the examination of the early cases rendered possible the diagnosis of multiple myeloma during life by Bradshaw and others, and the diagnostic value of the urinary condition is greatly enhanced by the indefinite character of the other signs in many cases. Not in all cases of multiple myeloma is the Bence-Jones protein present in the urine.

The recognition of the substance in question presents no great difficulty when once its properties are known. It is distinguished from the ordinary proteins of albuminuria by its very low temperature of coagulation. The urine begins to show turbidity when warmed to 50° C., or even below that point, and between 50° and 60° C. a bulky flocculent precipitate appears, which clings with great tenacity to the sides of the test tube and rises up in the froth which is abundantly formed. Further heating, especially after a few drops of acetic acid have been added, causes the precipitate to be redissolved, but some turbidity usually persists. The degree of clearing which occurs as the boiling point is approached varies, and depends, as Magnus Levy has shown, rather upon the presence of other substances in solution than upon any inherent property of the protein itself.

On cooling, the precipitate reappears, and by alternately heating and cooling the urine precipitation and re-solution may be indefinitely repeated. When the hot test tube is plunged into cold water, the appearance of the precipitate showering down through the cooling liquid is very striking and characteristic. If the cold nitric acid test be alone employed the substance may easily be mistaken for albumin, as a similar white ring is formed. With salicyl-sulphonic acid, picric acid, and other reagents employed for the detecting of proteins, precipitates are formed which disappear more or less completely on heating. With hydrochloric acid a dense precipitate is obtained.

The behavior of the precipitates obtained with various reagents naturally led to the inclusion of the Bence-Jones protein among albumoses, and in the hetero-albumose group, but the researches of Magnus Levy and others, which have included a study of the products of its disintegration by digestive ferments, have left no doubt that it is more correctly to be classed as an albumin. In some instances, as in one described by Bradshaw, some of the protein is spontaneously precipitated; the urine appears milky when passed and may throw down a deposit.

Although its connection with multiple myeloma is so well established, the mode and place of origin of the Bence-Jones protein remain unsolved problems. One naturally looks to the diseased bone marrow as the most probable seat of formation, but the quantity found there has been very small, and Magnus Levy estimates that the daily output corresponds in quantity to a large fraction of the total protein of the diseased marrow. He was rather inclined to refer its origin to a deranged metabolism of the food pro-

teins, but the output is apparently not influenced by diet, and there is no positive evidence in support of this view. Simon, on the other hand, is inclined to look to serum albumin as its parent substance.

Albumosuria and Peptonuria.—Some confusion surrounds the use of the terms albumosuria and peptonuria. Whereas some confine the name albumosuria to the excretion of the Bence-Jones substance, which, as we have seen, is not really an albumose, and speak of the excretion of proto- and deutero-albumoses as peptonuria, others, employing the name peptone in Kuhne's more restricted sense as a designation for the only protein which is not precipitated by saturation of its solutions with ammonium sulphate, speak of the excretion of proto- and deutero-albumoses as albumosuria. It is only recently that Kuhne's peptone has been found in the urine by Ito.

Although the excretion of proto- and deutero-albumoses is by no means rare it is not a conspicuous phenomenon from the clinical standpoint, and the quantities excreted are in no way comparable with those of the Bence-Jones protein found in cases of multiple myeloma. Moreover, the characteristic reactions are frequently masked by the simultaneous presence of albumin. Only comparatively rarely is a considerable quantity of albumose recognizable by the employment of the ordinary albumin tests.

The albumoses are not precipitated by heating after the addition of a few drops of acetic acid. Many albumin test reagents precipitate them, and the precipitates formed are cleared by heating. The addition of nitric acid in the cold, of picric acid, and of potassium ferrocyanide and acetic acid produces precipitates which behave in this manner. When nitric acid is used error may arise by the formation, in a concentrated urine, of a colorless precipitate of uric acid which is dissolved on heating and forms again on cooling; but any doubt may be cleared up by diluting the urine before the test is applied.

Salicyl-sulphonic acid is a very satisfactory reagent for the detection of albumoses in the absence of albumin. The precipitate which forms when a few drops of a saturated solution of the acid are added to the urine in the cold is soluble on heating. The reaction is a very delicate one and this reagent only precipitates proteins. For the detection of small quantities of albumose in the presence of albumin Devoto's method is perhaps the simplest. It is based upon the fact that when urine is saturated with ammonium sulphate, albumin and albumoses are alike precipitated. If, however, the saturated urine be boiled, the precipitate of albumin is thereby rendered insoluble in water, whereas that of an albumose is still soluble. The precipitate filtered off after boiling is therefore washed with water, and to the washings the tests for albumoses are applied.

The biuret reaction is often recommended for the detection of albumoses in urine, and may be conveniently applied as a ring test by gently pouring the urine upon the surface of a layer of cold Fehling's solution. If an albumose be present a pink ring will appear at the junction of the liquids, whereas an albumin yields a violet-colored ring. However, as Stockvis showed, this test is not reliable when it is applied to urine, since urobilin yields a similar pink tint. If the test be used care should at least be taken to exclude, by a preliminary spectroscopic examination, the presence of any considerable quantity of urobilin.

Albumosuria is met with when considerable quantities of protein material

are undergoing autolysis intra vitam, as, for example, in cases of acute yellow atrophy of the liver and of phosphorus poisoning and during the absorption of pneumonic exudates. During the rapid involution of the uterus after parturition a physiological albumosuria occurs. The albumosuria of fevers, which is usually slight in degree, may be ascribed to the increased protein breakdown which accompanies the febrile state, and that which accompanies extensive ulcerative lesions of the intestine is usually set down to the permeation of the ulcerated surfaces by albumoses from the alimentary canal.

True peptone was found in the urine by Ito, in association with other proteins, in cases of pneumonia and of tuberculous disease of the lungs.

Nucleohiston has been found in the urine of patients suffering from pneumonia and from some other febrile maladies, and also in a case of lymphatic leukæmia.

Sugars in Urine.—The excretion of a sugar in the urine, even in quantity sufficient to yield the ordinary reduction tests, is not necessarily a morbid event. Any healthy individual will excrete glucose provided that a sufficient quantity be taken, in one dose, by the mouth. The quantity usually required to bring about this result is from 150 to 200 grams, and in various morbid conditions the power of dealing with glucose is conspicuously lowered. Such alimentary *glycosuria ex saccharo* requires to be carefully distinguished from that which results from the free eating of starchy foods, *glycosuria ex amylo*, which is always a morbid event and represents the slightest degree of diabetes mellitus.

In young infants who are upon an exclusive milk diet, alimentary lactosuria is not uncommon, and a five-carbon sugar appears in the urine when as much as a liter of a fruit syrup is taken, the power of dealing with sugars of this class being comparatively small. Apart from such conditions and the excretion of lactose by nursing women, the excretion of quantities of sugar readily appreciable by the tests in ordinary use must be classed as a sign of disease, although traces of glucose are present, even in normal urines.

Glucose.—The question of the causation and significance of glycosuria is intimately associated with the study of diabetes, and has been fully discussed under that head.

Levulose.—After a sufficient dose has been taken by the mouth, levulose appears in the urine, just as glucose does under like conditions. However, the catabolism of levulose in the organism appears to follow a different path than that in which glucose is dealt with, and alimentary levulosuria has recently acquired a greatly enhanced clinical interest by the observations of H. Strauss and others, who have shown that the power of destroying this sugar is conspicuously impaired in various forms of hepatic disease. In this way a valuable test of the functional integrity of the liver is afforded.

It is a recognized fact that many diabetic subjects can utilize levulose far better than glucose, but the excretion of greater or less quantities of levulose in association with dextrose appears not to be uncommon in diabetes, and the amount of levulose is in rare instances nearly as great as that of dextrose. In such cases administration of levulose by the mouth has not increased the output of levorotatory sugar, and in a case of mixed mellituria, investigated by Otto Neubauer, glucose given by mouth was excreted in part as such, and in part as levulose.

To a quite different class belong the very rare cases in which levulose is excreted alone in the urine, one of which was most thoroughly studied by

Otto Neubauer, who recovered the sugar in crystalline form. A diet free from carbohydrates caused disappearance of the sugar from the urine, but tolerance for starch, and even for glucose, was in no way diminished. Even inulin, which stands to levulose in the same relation as starch does to glucose, caused no obvious increase of the output, which was wholly determined by the presence in the food of levulose as such, or in combination with glucose as cane sugar. Any administration of levulose was followed by its appearance in the urine, but whatever the quantity taken, from as little as 3.8 to as much as 50 grams, approximately the same fraction of the total, about 15 to 17 per cent., appeared in the urine unaltered. Suitable dieting, based upon these observations, brought about a conspicuous improvement in the patient's condition.

Lactose.—The excretion of lactose during lactation is a familiar event, and attains its maximum when for any reason nursing is suddenly arrested. Again, as has already been mentioned, alimentary lactosuria is not uncommon in young infants. Lactosuria has no pathological significance, but is one of those harmless conditions which require to be borne in mind, lest a wrong interpretation be put upon them. Laiose, maltose, and isomaltose have also been detected in urine, but their presence has no clinical import so far as is known.

Pentoses.—The sugars which contain five carbon atoms in chain, instead of six, are abundantly present in plants, but it is only of recent years that members of the group have been recognized as constituents of animal tissues, and rarely in the urine.

Pentoses in considerable amounts may be introduced into the alimentary canal in vegetable foods, and as the power of the organism to destroy such sugars is much less than in the case of the members of the hexose group, they not infrequently are excreted in appreciable quantities after the free eating of certain fruits, such as plums and cherries, when beer is freely drunk, or as von Jaksch has pointed out, when quantities of the prepared fruit juices which are popular beverages on the continent of Europe are taken. Again, in some cases of diabetes traces of pentose have been detected in the urine, but the nature of the pentose present has not yet been determined.

In certain rare cases the excretion of a pentose to the amount of several grams per diem persists year in and year out, and perhaps throughout life, without any obvious detriment to the patient's health. In such cases the sugar excreted, which is racemic, *i. e.*, optically inactive, arabinose, is clearly not derived from vegetable foods, for the arabinose present in these is optically active. Moreover, the excretion is wholly unaffected by the withdrawal of carbohydrates from the diet, and the source of the urinary pentose is still very obscure. Carl Neuberg has suggested, on chemical groundse which are too technical to be discussed here, that the parent substance is galactose. This sugar is found in the brain, and its abundant presence in milk in combination with glucose, as lactose, bears witness to the existenc- of a seat of its manufacture in the organism. A pentose exists in nucleo, proteins, and is specially abundant in the thymus, but this is a different sugar, l-xylose, and, moreover, thymus feeding is without effect upon the urinary output in these cases of persistent pentosuria.

It is probable that pentosuria, which is a rare anomaly, and apparently a harmless one, occurring in families, many of which are of the Jewish race, should be classed with such sports of metabolism as alkaptonuria and

cystinuria. Its clinical importance lies in the fact that those who exhibit the anomaly are usually looked upon as diabetics, and are treated as such; whereas the dread which is inspired by the diagnosis of diabetes, and the irksome dietary restrictions which are imposed, are in these cases unnecessary and not called for.

Glycuronic Acid.—Although not a sugar, glycuronic acid has such intimate chemical relationships with the members both of the hexose and pentose groups that it calls for mention, in this place, among the reducing substances which are met with in urine. It is excreted in combination with a variety of ingested substances, such excretion being the outcome of a protective mechanism by which the substances in question are rendered harmless and escorted out of the body. Thus, the presence of a compound glycuronic acid is no more a pathological event than that of hippuric acid, in which glycocoll fulfils a similar function, and its explanation is to be sought in the excretion of the substance combined, rather than in any disturbance of metabolism. Whether or not glycuronic acid is a normal intermediate product in the catabolism of glucose is still an open question. It is derived from glucose by the oxidation of the alcohol grouping in the molecule, whereas the aldehyde grouping, to which the reducing power is due, remains unaffected. Emil Fischer is inclined to think that the noxious substance is primarily combined with glucose, and that the oxidation to glycuronic acid is effected later.

Although the acid itself is dextrorotatory, the compound glycuronates met with in urine are levorotatory. They differ greatly in their stability; some, such as menthol glycuronic acid, undergo spontaneous decomposition in urine. Among substances the administration of which leads to the excretion of considerable amounts of the conjugated glycuronates are chloral, morphine, camphor, and copaiba, but even apart from drugs and foods the protective mechanism is called into play, and traces of indoxyl glycuronate, and perhaps others, are met with in normal urine.

Recognition of Sugars in Urine.—It must not be forgotten that the ordinary chemical tests for substances of this class, such as Trommer's, Fehling's, and Nylander's tests, merely afford evidence of the presence in the urine of a reducing substance which may or may not be a sugar. It is only by the employment of further methods that certainty upon the point may be obtained, and that the particular kind of sugar which is present can be determined.

In actual practice, if a conspicuous reduction occurs when hot Fehling's solution is added to hot urine, neither liquid actually boiling, there is little chance of error in making the diagnosis of glycosuria. When reduction is only obtained after boiling the mixture for some time, or when it is cooling, the evidence is not conclusive, especially if a pea-green opacity alone develops. Such a reaction may be, and often is, due to the presence of a small quantity of glucose, but it may also result from other causes, and confirmatory tests are necessary. In concentrated urine slight reduction may be brought about by uric acid and kreatinin, or by salicyluric acid, when salicylates are taken as drugs. Sugars other than glucose may give rise to error and of these lactose is the commonest. With lactose the reduction is less prompt than with glucose, and does not occur below the boiling point; however, the class of cases in which lactosuria occurs is a very restricted one.

Levulose cannot be distinguished from glucose by the copper tests. There is a consensus of opinion that in cases of pentosuria the reduction

is usually delayed, and is apt to occur suddenly during cooling. However, Bial denies that this is a characteristic of fresh pentose urines, and has seen the reduction occur before the boiling point is reached. As a rule, in pentosuria the reaction is of such a degree as that yielded by 0.5 per cent. of glucose.

The compound glycuronates reduce copper, but not all with equal readiness. Homogentisic acid reduces Fehling's solution readily, but to anyone familiar with alkaptonuria the darkening of the liquid when heated with the alkaline reagent, a change which precedes the reduction of the copper salt, at once suggests the true diagnosis. In carboluria a slight reduction occurs after boiling for some time, and is attributed to hydroquinone, which is excreted in combination with sulphuric acid, by which combination its characteristic reactions are masked.

The *polarimeter* affords important information as to the presence and nature of sugars in urine. A strong dextrorotatory effect is highly suggestive of glucose, but lactose is also dextrorotatory. Levulose is, of course, levorotatory, and when present in association with glucose it counteracts to some extent, and may even completely balance, the dextrorotation due to the latter sugar. This fact renders the quantitative estimation of glucose in urine by means of the polarimeter uncertain, and may explain discrepancies between the results so obtained and those of the reduction methods. In a similar manner the rotatory effect of glucose may be partly masked by the presence in abundance of the levorotatory β-oxybutyric acid, which plays so important a part in the causation of diabetic coma.

The only sugar met with in urine which is actually optically inactive is the racemic arabinose of true pentosuria, whereas the arabinose of alimentary pentosuria, which is derived from vegetable foods and drinks, rotates the polarized ray to the right, for the names l-arabinose and l-xylose express their chemical relationships and not their optical properties. The urine is also optically inactive in alkaptonuria. Glycuronic acid is dextrorotatory, but the compound glycuronates which are met with in urine have a levorotatory action. By boiling the urine with hydrochloric acid the compound glycuronates are broken up and the original levorotation is replaced by the dextrorotation of the freed glycuronic acid.

To sum up, dextrorotation of a urine which contains a reducing substance indicates the presence of glucose, unless the conditions are such that lactosuria may be present. Levorotation may be due to levulose, or to compound glycuronates. If the urine be optically inactive there may be balancing quantities of glucose and levulose, or the sugar may be a pentose, or again the reducing substance may not be a sugar at all.

Further and most important information is supplied by the fermentation test. Whereas glucose and levulose are readily fermented by yeast, lactose, being a disaccharid, is not fermented until it has been split into dextrose and galactose, and no fermentation occurs within the twenty-four hours usually allowed for the test. The pentoses do not undergo fermentation, and the compound glycuronates also resist the action of yeast. In performing the test it should be remembered that the action of yeast is inhibited by exposure to too high a temperature, and mistakes have ere now arisen from such overheating.

Thus a further means of discrimination is afforded. A levorotatory reducing substance which is removed by fermentation is presumably levu-

lose, as the compound glycuronates are not destroyed by yeast. If a dextrorotatory urine becomes levorotatory after fermentation, the levorotation is probably due to β-oxybutyric acid, the glucose having been destroyed. If the reducing power is absent after fermentation from a urine which was originally optically inactive, a balanced admixture of dextrose and levulose may be suspected. A dextrorotatory sugar which does not ferment is presumably lactose, and when dextrose and pentose are present in association the former will be destroyed by fermentation, and the urine which still retains the reducing power of the pentose will now be optically inactive.

A reducing substance which is optically inactive, and does not ferment, may be pentose (racemic arabinose) or some of the reducing substances which are not sugars, of which the most potent is homogentisic acid.

The phenylhydrazine test also supplies valuable indications which help in the differentiation of sugars. When a crystalline product is obtained it is practically significant of the presence of a sugar. It is true that glycuronic acid forms such a compound, but the conjugated glycuronates do not. However, some of the compound glycuronates, such as that of menthol, are very easily decomposed, and the possibility that the crystals obtained are formed by the liberated glycuronic acid cannot be wholly excluded. A few osazone crystals are not of great significance owing to the extreme delicacy of the test, which is capable of detecting traces of sugar within physiological limits. If the osazone obtained be purified by recrystallization, and its melting point determined, this affords important information as to the nature of the sugar present.

Dextrose and levulose yield the same osazone which melts at 205° C. Lactose forms an osazone which melts at 200°, but owing to its greater solubility and the small amount of lactose which is usually present in urine, no crystalline product is usually obtained when the test is applied in cases of lactosuria.

Pentosazones, which are easily obtained, may be recognized by their much lower melting point, between 150° and 160° C., and the final diagnosis of pentosuria should not be made until a crystalline product of such a melting point has been obtained.

For the discrimination of special sugars certain substituted phenylhydrazines are of value. Thus, Neuberg obtained, by the use of methylphenylhydrazine, a compound with levulose which melted at 153° C., and the same observer has shown that, with parabromphenylhydrazine, glycuronic acid yields a crystalline compound which melts at 236° C.

Special tests for certain sugars are also of value. Pentose and also glycuronic acid yield furfurol reactions. For the detection of pentoses Bial's modification of the orcin test is especially useful. The reagent is prepared by dissolving 1 gram of orcin in 500 cc. of hydrochloric acid of a specific gravity of 1.151; 20 to 30 drops of a 10 per cent. solution of ferric chloride are afterward added. The reagent should be kept in a yellow glass bottle. In testing, 5 cc. of the reagent are heated to boiling in a test tube; after the tube has been removed from the flame, and boiling has ceased, five drops of the urine to be tested are added from a pipette. If pentose is present a rich green color appears at the junction of the urine and reagent, and spreads through the liquid when it is shaken. On examining with the spectroscope a dark absorption band is seen between the solar C and D lines. A second band which is usually seen in the extreme red has no diagnostic importance.

It is claimed for this test that when performed in the above manner it is yielded by no urines save those which contain pentose, and the writer's experience confirms this. If, however, the urine and reagent be boiled together, the green color and the characteristic absorption band appear if the urine contains a compound glycuronate. Exact care in preparation of the reagent is necessary, and its efficiency should be tested with a solution of a pentose, or with a pentose urine if such be available.

Further evidence is afforded by the phloroglucin test, which is also yielded by glycuronic acid, and confirmation is obtained by preparing a crystalline osazone which, after recrystallization, melts at 150° to 160° C.

Tollens' phloroglucin test is as follows: The urine is boiled with hydrochloric acid of 1.19 specific gravity, to which a knifepoint of phloroglucin has been added. If pentose be present a deep cherry-red color develops, and a dark flocculent precipitate forms. If the precipitate be filtered off and treated with alcohol it yields a violet-colored solution, which shows an absorption band between the D and E lines.

For the recognition of lactose Rubner's test may be employed. The urine is boiled for several minutes with an excess of neutral lead acetate; on addition of ammonia a red color develops, and a cherry-red precipitate falls.

Levulose differs from other sugars in yielding Seliwanoff's reaction. The test is carried out as follows: 10 cc. of urine are warmed with a little resorcin and 2 cc. of dilute hydrochloric acid. If levulose be present the liquid assumes a red color, and deposits a precipitate which is soluble in alcohol, forming a rich red solution.

Substances of the Acetone Group.—The substances grouped together under this name which appear in the urine, β-oxybutyric acid, aceto-acetic acid, and acetone, are closely related to each other and form a natural series. It is usually held that β-oxybutyric acid is only excreted when large quantities are being formed, and in association with aceto-acetic acid and acetone. When a lesser production is going on the two latter members of the group alone appear, whereas when the quantities are very small acetone alone is present in the urine. Even in health minute amounts of acetone are found.

The most important cause of the formation of the acetone substances is apparently the withdrawal of carbohydrates from the food, or inability to burn carbohydrates, as in diabetes. Thus starvation or a carbohydrate-free diet excites acetonuria even in normal individuals, and in the cases of persistent vomiting in which it is a prominent symptom the acetonuria may be due to this same cause. In a variety of morbid conditions in which there is an abnormal tissue breakdown acetonuria is met with, such as fevers, carcinomas, phosphorus poisoning; and cyclic vomiting, pernicious vomiting in pregnancy and delayed chloroform poisoning must be included among the conditions in which acetonuria plays an important part. In delayed chloroform poisoning, and also in fatal cases in children, in which vomiting is almost the only other symptom save acidosis, advanced fatty changes have been met with in the liver, by Guthrie, Langmead, and others. Speaking generally, acetonuria appears to be more easily induced in children than in adults, and is not uncommon in association with bronchopneumonia. The view usually held at the present day ascribes the phenomena of diabetic coma to poisoning by these substances, and especially by oxybutyric acid,

which, however, produces its effects as an acid, and not in virtue of any specific toxic properties.

It used to be held that the parent substances of the acetone group are the proteins of the body, but the investigations of Magnus Levy, who showed that the protein breakdown was quite unequal to explaining the enormous quantities of β-oxybutyric acid sometimes excreted in the urine, and that the excretion of this acid in no way runs parallel with the total nitrogen output, proved that some other source must be looked for, namely, the fats. This has been confirmed by the demonstration that a diet rich in fats causes an increased acetonuria, especially if the fatty acids present are oleic or other lower members of the fatty acid series.

Still more recently the experiments of Embden and others on the production of acetone from certain amino-acids, leucin, tyrosin, and phenyl-alanin, when these were perfused through the liver, seem to indicate clearly that since acetone is formed from these protein fractions, the proteins of the food and tissues must be looked upon as contributing to the total yield of the substances of the acetone group.

The most important member of the group, β-oxybutyric acid, is the least easy of detection. A rough idea of the amount present may be obtained from the degree of levorotation which the urine exhibits after fermentation with yeast, but in order to obtain any accurate notion of the quantity present, it is necessary to extract the acid by methods which can hardly be classed as clinical; or to convert it into α-crotonic acid and to estimate it as such. Again, estimations of the urinary ammonia afford a rough indication of the amounts of abnormal acids, β-oxybutyric and aceto-acetic, which are being excreted in combination with it.

The presence of aceto-acetic acid is indicated by the well-known iron reaction, namely, the development of a deep red-brown color on the addition of a solution of ferric chloride. This test serves to indicate an increase of the substances of the group, and the presence of a higher member of the series than acetone. It therefore affords a very valuable indication that the morbid processes which result in the formation of these substances are actively at work. When patients are taking a salicylate or aspirin this reaction is, of course, masked by the iron reaction due to the drug. When doubt arises whether the color obtained is due to aceto-acetic acid, it may be dispelled by boiling the urine for a few minutes and repeating the test after it has cooled. As a result of such treatment aceto-acetic acid will be broken up into acetone and carbon dioxide and the reaction will no longer be obtained. For the detection of acetone the tests usually employed are those of Lieben and of Legal, both of which are easy of clinical application.

A convenient modification of Lieben's test is carried out as follows. To a few cubic centimeters of liquor potassæ a watery solution of iodine with iodide of potassium is added until the liquid remains faintly tinted. Some urine is then allowed to flow gently upon its surface along the side of the test tube. If acetone be present a yellowish-white cloud develops at the line of junction of the liquids, and the characteristic odor of iodoform is readily detected. Tincture of iodine must not be used, as the alcohol present therein itself yields iodoform. When liquor potassæ is added to the urine, and afterward a solution of sodium nitroprusside, a deep red color appears whether the urine contain acetone or not. If acetone be present acidification with acetic acid causes a change of color through carmine to violet or purple. In the

absence of acetone the liquid is decolorized by excess of acetic acid and appears yellow.

Lipuria.—The excretion of fat in the urine in quantities which are appreciable to the eye is a decidedly uncommon symptom. In forms of renal disease in which the kidneys undergo a so-called fatty degeneration, such as chronic parenchymatous nephritis, the microscope shows fat globules in shed epithelial cells and in casts, and even free globules or crystals of fat may be present. In chyluria the milky appearance of the urine is due to the presence of minute fat particles. In cases in which malignant growths of the kidneys were breaking down larger quantities of fat have occasionally been detected in the urine.

Apart from these local forms of lipuria, there are others in which lipuria is an outward sign of lipæmia, and in any condition in which there is an accumulation of fat in the blood it may find its way into the urine.

Even the administration of large quantities of fat by the mouth in the form of cod-liver oil, or of olive oil given for the treatment of gallstone trouble, may give rise to lipuria. During pregnancy the excretion of fat has been observed and a lipuria of moderate degree may be met with in cases of diabetes mellitus, phthisis, and other conditions attended by rapid wasting, acute yellow atrophy of the liver, and phosphorus poisoning. Fractures of long bones and the operation of osteotomy may be followed by the escape of fat into the blood, as is witnessed by the phenomenon of fat embolism, and may give rise to a considerable lipuria.

In any case in which the urine is found to contain fat it is important to exclude accidental or intentional admixture, as by the use of an oiled catheter or the addition of milk to the urine after it has been passed. In true lipuria the fat may form an emulsion, as in chyluria, or may form a cloud suspended in the liquid, or an oily and transparent or an opaque layer upon its surface. By shaking the urine with ether the contained fat may be extracted, leaving the liquid clear and transparent when the layer of ether has separated from it. When a drop of the ethereal extract is allowed to evaporate on filter paper it leaves a translucent greasy mark. The minute globules in the sediments may be recognized with greater certainty by staining with osmic acid.

It should be mentioned that calculi composed of fats have, very rarely, been formed in the urinary passages. The suggestion that in such cases the fat has been introduced per urethram in the form of bougies or otherwise is certainly not tenable in all instances, and Horbaczewski's investigations suffice to establish the reality of urostealiths beyond all reasonable doubt. The fatty calculi have usually been coated with a layer of earthy phosphates. As to the significance of such calculi and the nature of the morbid processes in which they have their origin we are still completely in the dark. Not more than five or six such calculi are on record.

Choluria.—In cases of jaundice the bile pigment very early finds its way into the urine, and its presence therein may be recognized by the appropriate tests and by the color which it imparts. Uric acid crystals deposited from icteric urines have a leathery brown color when viewed in bulk, and under the microscope the individual crystals are seen to be modified both in tint and in form by the included bile pigment.

Gmelin's test is best carried out by allowing the urine to flow gently on to nitric acid in a test-tube. A play of colors is seen at the junction of the liquids, and the whole of the layer of urine often acquires a lasting green

tint. It is necessary that the green color of biliverdin should be obtained, as the chromogens of urine may yield pink or purple rings under the same conditions. Maréchal's test is also easily obtained and conclusive. Some tincture of iodine is allowed to flow upon the surface of the urine in a test tube, and a green ring colored by biliverdin appears at the junction layer if bile pigment be present.

In some cases the amount of bile pigment is so small that the above tests yield inconclusive results. In such circumstances Huppert's test is of great value. Any required quantity of the urine may be precipitated by the addition of milk of lime or of barium chloride and hydrate. The precipitate, which carries down with it all the bile pigment present is collected upon a filter and transferred to a beaker containing alcohol acidified with sulphuric acid. When the beaker is heated upon the water-bath the bile pigment is converted into biliverdin, which imparts to the acidulated alcohol a rich green color.

Any condition which produces jaundice may cause the appearance of bile pigment in the urine, but the choluria may disappear whilst the skin is still conspicuously bile stained. In a very few cases which may be classed as clinical curiosities, the urine has been deeply bile stained, although no jaundice existed. In such cases a fistulous communication has existed between the biliary and urinary passages.

The bile salts, like the pigments, are met with in the urine in jaundice, but far less constantly, usually only in the early days of the attack and in no large quantities. It was formerly believed that the presence or absence of bile salts afforded an indication whether the jaundice was hepatogenous or hæmatogenous, but in recent years it has become evident that all jaundice is due to obstruction either of the larger or smaller biliary passages, and it has been shown that in toxic forms of jaundice, such as that produced in animals by toluene-diamine, bile salts are excreted in the urine. The evidence available tends to show that the formation of the bile salts is inhibited when biliary obstruction occurs, and it is certain that no such quantities of these substances are found in the urine as might be expected if the normal quantities present in the bile were being absorbed. Nor do experiments on the injection of bile salts into animals favor the supposition that they are destroyed to any great extent in the organism.

Pettenkofer's test is not applicable for the detection of the bile acids in urine, owing to the fact that indican and other constituents contribute to the production of a red color which closely simulates the true reaction.

For clinical purposes the best test available is based upon the conspicuous lowering of surface tension which results from the presence of bile salts in solution. A finely divided, light powder, such as flower of sulphur, is scattered upon the surface of the urine. Under ordinary conditions such a powder remains resting upon the surface of the liquid, but if bile salts be present it rapidly sinks to the bottom.

The Chemical Protective Mechanisms.—In adapting itself to its environment the organism has acquired means of protecting itself against various chemical poisons which may be present in the food, or may be developed by the action of the intestinal bacteria. When these mechanisms are called largely into play the products of their working are to be found in the urine.

The means of protection against acids in excess has already been re-

ferred to. For their neutralization ammonia is intercepted on its way to form urea, and in this way the drain of fixed alkalies from the blood and tissues, which would otherwise result, is to a great extent averted. Hence the amount of ammonia excreted in the urine affords an index of the extent to which this process is at work, and the greatly increased output of this base in cases of acidosis is readily explained. It is even probable that the increased excretion of ammonia and the diminished excretion of urea in certain grave forms of liver disease, such as acute yellow atrophy, is due rather to the formation of abnormal quantities of fatty acids than to loss of power of the diseased liver to effect the conversion of ammonia into urea. Münzer has shown that in phosphorus poisoning the administration of sodium bicarbonate conspicuously diminishes the ammonia output, and such an effect is held to indicate that the excess of ammonia, which is thus restricted, is due to acidosis.

Vegetivorous animals, such as rabbits, which, from the nature of their diet, are little exposed to risks of acid poisoning, appear not to have developed this protective mechanism, for the administration of acids to such animals does not give rise to any increased excretion of ammonia.

With few exceptions the benzene rings of aromatic compounds are not broken up in their passage through the organism. The aromatic fractions of proteins, tyrosin, phenyl-alanin, and tryptophane constitute the exceptions, special paths being provided for their catabolism. Several mechanisms are provided for the harmless disposal of aromatic compounds, of which the most important is combination with sulphuric acid, either with or without preliminary oxidation. Hence it comes about that when aromatic substances other than the proteid fractions and their direct derivatives are taken in excess, the aromatic sulphates of the urine, which normally constitute about one-tenth of the total sulphates, are greatly increased, and in such conditions as carboluria it is found that practically all the sulphuric acid is in such combination. Folin has recently thrown doubt upon this interpretation of the significance of the aromatic sulphates, which, on account of their approximately constant amounts on protein-rich and protein-poor diets respectively, he regards as being probably products of tissue metabolism. However, in face of the accumulated evidence on the other side, this cannot yet be regarded as proven.

Some portion of the aromatic substances of the food, and of those formed from food substances in the alimentary canal, as well as other non-aromatic poisons, are excreted in combination with glycuronic acid as compound glycuronates. It often happens that an aromatic poison is excreted in part as an ethereal sulphate and in part as a compound glycuronate.

The familiar fact that benzoic acid taken by the mouth is excreted in combination with glycocoll, with the loss of water, in the form of hippuric acid, was the earliest recognized example of a synthetic process in the animal body. This illustrates yet another mechanism for the protection of the organism from aromatic poisons, and a variety of benzene derivatives akin to benzoic acid, such, for example, as salicylic acid, follow this protective path, being excreted as compounds of similar structure to hippuric acid.

Even in health the mechanisms referred to are at work to some extent, as witness the aromatic sulphates which are constantly present in the urine, and also the trace of glycuronic acid, which is probably, for the most part, combined with indoxyl.

CHAPTER IV.

URÆMIA.

By A. E. GARROD, M.D., F.R.C.P. (Lond.).

The name uræmia is used to designate a group of symptoms which usher in the fatal ending in a large proportion of cases of renal disease. The group embraces a large number of morbid manifestations of widely different characters, only a few of which are usually observed in any individual case, and which assume such diverse grouping that two cases which may, without hesitation, be designated uræmic, may, in their superficial aspects, show little in common.

The boundaries of the symptom complex are somewhat ill defined, and whereas some authorities would limit the application of the term uræmia to functional disturbances which appear to have a toxic origin, others would extend its signification as to include a number of anatomical lesions such as ulceration of the stomach and intestines, stomatitis, and pericarditis; whilst others again regard as minor uræmic phenomena the cardiovascular changes which play so conspicuous a part in chronic renal disease.

Impairment of the renal functions, whatever may be its cause, may bring about a condition of uræmia, provided always that both kidneys are implicated; but it is one of the most puzzling features of the condition, and one which opposes the chief obstacle to any satisfactory explanation of its pathology, that complete arrest of the excretory functions of the kidneys, although necessarily fatal unless relieved by surgical measures or otherwise, does not lead to the manifestation of the more characteristic uræmic symptoms.

Unilateral renal disease, even though it result in such complete destruction of the affected kidney as follows the permanent occlusion of one ureter by a calculus, does not give rise to uræmia, provided always that the remaining kidney adequately performs its functions. On account of the protean aspects which uræmia assumes, an attempt to describe in detail the features of individual attacks entails needless repetitions, and it will, therefore, be more convenient to begin by considering the various manifestations of the uræmic state in turn, and to group them according to the several systems—nervous, alimentary, circulatory, and respiratory—to which they are referable.

Pathology.—The Condition of the Urine.—In the majority of instances the onset of uræmia is preceded by diminished excretion of urine, and if the scanty urine be of low specific gravity the danger of uræmia is the more obvious. In some cases the quantity of urine passed is not below the normal, but when this is the case its specific gravity is usually low. Side by side with a fall of specific gravity goes an elevation of the freezing point, both phenomena being alike dependent upon a decrease of solids in solution.

Albumin is practically always present in the urine of uræmic patients, but the quantity varies greatly according to the nature of the primary renal lesion.

Casts may or may not be present. The output of urea and of the total nitrogen of the urine has been found to be conspicuously diminished during the days preceding an attack, whereas during and immediately after the attack the excretion may be distinctly increased. An increased excretion of ammonia bears witness to some degree of acidosis.

The Condition of the Blood.—In almost all cases uræmia is accompanied by a conspicuous increase of the molecular concentration of the blood. This is evidenced by a conspicuous depression of the freezing point of the serum, which, under ordinary conditions, is much more constant than that of the urine, and varies but little from —0.56° C. However, cases have been met with in which the molecular concentration was little marked, suggesting that the accumulation of waste products in bulk is by no means the only factor at work. On the other hand, a greatly increased molecular concentration of the blood may exist apart from the development of any uræmic symptoms.

Rose Bradford has found that in cases of obstructive suppression of urine the accumulation of waste products in the blood is much less than in cases of ordinary uræmia. This may be due to the occurrence of an increased breaking down of proteins as one of the phenomena of the uræmic state, but it is conceivable that with complete anuria there may be a restriction of catabolism, comparable with the apparent inhibition of the formation of bile acids in obstructive jaundice.

The molecular concentration in the blood is mainly due to an accumulation of the nitrogenous products of the breaking down of proteins, as is shown by the conspicuous increase of residual nitrogen; that is to say, of nitrogen other than that contained in the blood proteins. This has been clearly brought out by the researches of H. Strauss[1] carried out in Senator's clinic. At the same time no increase is apparent of inorganic salts, such as sodium chloride. The same lesson is taught by the more recent researches by physical methods; for the great depression of the freezing point of the blood, which is almost constant in association with uræmia, is not attended, as Bickel and others have shown, by any increase of electrical conductivity, such as would be observed if the molecular richness were due to an increase of dissociable molecules, such as those of salts.

Urea is found in considerable quantities in various secretions and excretions of uræmic patients such as the gastric juice, intestinal contents, bile, saliva, and sweat, and in some cases the sweat as it evaporates leaves an efflorescence of crystals of urea upon the skin of the patients.

Theories of Uræmia.—In the earlier days of the study of uræmia the symptoms grouped under that name were ascribed by Traube and others to such causes as œdema of the brain or disturbances of the cerebral circulation. Such views have met with little acceptance in recent years, and the characters of the uræmic manifestations are so strongly suggestive of a toxic origin that investigators have, for the most part, sought to explain them as the results of the accumulation in the blood of a poison or poisons. The obvious association which exists between uræmia and deficient functional activity of the kidneys naturally suggested that the toxic material might be found among the end products of metabolism, which it is the function of the kidneys to excrete; but in spite of the large amount of patient research

[1] *Die chronische Nierenentzündungen*, Berlin, 1902.

which has been expended upon the problem, from the days of Bright and Addison down to the present, no solution yet proposed has met with general acceptance, and the cause still remains unknown.

The very name uræmia, which, like so many other incorrect designations, has become so firmly established that to attempt to replace it would be alike futile and pedantic, is a legacy of the earliest of all the toxic theories, that which ascribed the train of symptoms to poisoning by urea. It was long ago clearly demonstrated that this theory was untenable, seeing that urea is almost devoid of toxic properties, and may be injected into animals in large doses without exciting any conspicuous symptoms. A similar fate befell the well-known theory of Frerichs, who ascribed uræmia not to urea itself, but to ammonium carbonate formed from it within the organism by the action of a ferment; and Treitz's modification of that theory, according to which the change from urea to ammonium carbonate was brought about in the alimentary canal, for it was shown that an increase of ammonia in the blood is no constant or conspicuous feature of uræmia. The theory of kreatinæmia also failed to win any general acceptance, nor has it been found that any one of the end products of protein catabolism fulfils the necessary requirements.

In view of this failure to identify, among the normal excretory products, any single toxic agent capable of explaining the symptoms observed, not a few physicians have been led to adopt the view that some intermediate product of metabolism may be responsible. Of such carbamic acid has most in its favor, in view of the phenomena observed in animals with an Eck fistula. Others again hold that the manifestations are rather the results of the retention of the excretory products generally, than of the specific toxic action of any one of them. However, a great obstacle to the acceptance of this last view is the fact that the more characteristic symptoms are not seen in cases of complete anuria, in which the kidneys excrete no waste products at all.

Among the older theories, that of Bouchard, which was based upon the toxic effects which are observed when urine is injected into the circulation of animals, calls for special mention. The fatal effects of such injections, provided that enough urine be employed, are beyond question, and, in the light of more recent investigations, they appear to be largely due to the toxic action of potassium salts. Thus, Herringham found a close correspondence between the degrees of toxicity of the urines and the quantities of potassium salts contained in them, and other observers have obtained like results. However, opinions are not unanimous on this point, and Charrin and Roger failed to trace such a correspondence.

Various organic constituents of urine, such as kreatinin and the pigments, have been shown to be incapable of producing the observed toxic effects, at any rate in such quantities as are contained in the injected urine, whereas much of the toxic power is retained by the inorganic constituents of the ash.

Bouchard found that the urine of patients with uræmia was conspicuously less toxic for rabbits than was normal human urine, and this observation supplied the strongest argument which could be adduced for the applicability of the results of toxicity experiments. He attributed the uræmic symptoms mainly to organic toxic substances which are constituents of normal urine, but which he identified only by their physiological action, but admitted that some portion of the poisonous effects of injected urine

was due to potassium salts. Of the toxins, one induced convulsions, another depressed the temperature, another exerted a narcotic action, and yet another contracted the pupils. Bouchard's urotoxins still remain theoretical substances, and his conclusions have failed to obtain acceptance from more recent investigators in the field, although no one can fail to admire the elaborate researches upon which they are based.

The unquestioned toxicity of potassium salts formed the basis of the theory of Feltz and Ritter,[1] who attributed uræmia to their action. In support of their theory they brought forward a mass of valuable experimental results, which included demonstrations of the inability of various organic constituents of the urine to induce uræmic symptoms. This theory has nevertheless shared the fate of so many others, and later investigators have failed to trace any direct relationship between accumulation of potassium salts in the blood and the development of uræmia. Nor are the toxic effects of potassium salts at all strictly comparable with the phenomena of that condition.

The failure which has hitherto attended all attempts to explain the phenomena of uræmia by the toxic action of any one constituent of the urine, or any combination of excretory products, has led a number of more recent investigators to look for an explanation in other and fresh directions. Thus, a physical theory has been propounded which attributes the effects to the mere accumulation of molecules in the blood, a molecular overcrowding so to speak, rather than to any specific toxic action of particular molecules. The name of Lindemann is specially connected with this view. It would appear, however, that uræmia occasionally develops apart from any excessive molecular concentration, and in cases in which the freezing point of the blood is conspicuously depressed, symptoms of uræmia may be wholly absent.

Some investigators have suggested that the kidneys produce an internal secretion which may play an important part in controlling metabolism. Thus, Brown-Séquard found that animals succumbed more quickly after removal of the kidneys than after ligature of the ureters. Ascoli, who has confirmed this observation, ascribes the more rapid death to the loss of the internal secretion of the organs, and in support of this theory he adduces experiments in which the injection of the juice of normal kidneys into animals deprived of their kidneys prolonged life to the limit attained in animals with ligatured ureters.

Rose Bradford's well-known experiments upon dogs suggest that the removal of renal substance within certain limits, as, for example, one kidney and part of the other, causes increased output of water and of the end products of protein metabolism such as urea, and that this may be ascribed to the diminution of a controlling influence exerted by the kidneys upon the metabolic processes, with the result that metabolism runs riot. This would naturally lead to an overloading of the blood with waste products, beyond the accumulation resulting from mere retention. Moreover, Bradford has found, as has already been mentioned, that in cases of obstructive suppression in which the internal renal secretion might be supposed to be still yielded, the accumulation of waste products in the blood was less than in ordinary cases of uræmia.

On the other hand, it must be mentioned that Bainbridge and Beddard,

[1] *De l'urémie expérimentale*, Paris, 1881.

repeating Bradford's experiments with cats, did not constantly obtain an increased output of nitrogen, and regard the increase, when it occurs, as due to inanition, and of the same nature as that observed in starving animals.

Another recent theory is that which attributes uræmia to nephrolysins, a theory which has been advocated by Ascoli[1] and others. It has been shown that just as when bacteria find their way into the animal organism substances antagonistic to them are produced, so also when cells of a particular organ are injected *sub cutem*, or into the peritoneal cavity, substances antagonistic to the special cells injected are found in the organism. Of such products, which are collectively spoken of as cytolysins, those which are destructive of red blood corpuscles, the hæmolysins, have been most studied, but the nephrolysins have also attracted considerable attention. When broken-up renal substance is injected into animals, substances are found in the serum of the animals so treated which exert a destructive action upon the renal cells of other animals. When injected into a second animal such a serum sets up a nephritis and causes albuminuria, and the serum of the second animal, when injected into a third, has been found to excite a temporary albuminuria.

It has been suggested that the tendency to chronicity in renal diseases is due to the establishment of a vicious circle, and that the nephrolysins formed as a result of the renal lesions aggravate the morbid condition in the kidneys. It has, indeed, been shown that when nephritis is set up in an animal, by chromic acid or otherwise, the serum of the animal contains nephrolysins which are capable of causing nephritis in a second animal, but it has not yet been conclusively proved that the nephrolysins so formed react upon the kidneys of the animal itself. However, it has been stated that injury to one kidney, such as follows ligature of a ureter, tends to excite disease in the second kidney, but clinical experience of cases of unilateral obstruction by calculus does not appear to support this view. Ascoli also records experiments which point to the production of antinephrolysins in animals which are protected by the injection of minor doses of nephrolytic sera.

This observer and those who think with him believe that the phenomena of uræmia may result from the action of nephrolysins upon the nerve centres. There is evidence to show that the effects of cytolysins are not confined to the special tissues to which they are antagonistic, but may be more widespread. Moreover, Ascoli found that the injection of normal rabbits' serum into the subdural space of dogs produced no obvious effects, and even nephrolytic serum was sometimes equally innocuous; however, in some instances such sera excited general tonic and clonic convulsions, and deep coma ending in death.

Our knowledge of the nephrolysins, of their effects upon the kidneys of the animals in which they are primarily formed, as distinguished from those of other animals injected with the nephrolytic serum, and above all of the power of nephrolysins in the general circulation to excite the stormy symptoms of uræmia, is still too incomplete for any theory of uræmia in which they play the principal part to command acceptance. As Friedrich Müller has pointed out, the renal diseases in which uræmia is most apt to occur in its most pronounced forms are not always those in which the destruction of renal tissue is most extensive, and although, in cases of obstructive suppres-

[1] *Vorlesungen über Uraemie*, Jena, 1903.

sion, it may be that death results before the break-down of renal substance is sufficient to cause the appearance of abundant nephrolysins in the circulation, such an explanation will not apply to the absence of convulsions and coma in cases of anuria from thrombosis of the renal arteries.

Nevertheless, the theory in question calls for careful consideration, since it introduces new factors derived from a fresh field of study, and deals with classes of products which are still "seen through a glass darkly," the very existence of which was not even suspected until within recent years.

Meanwhile the cause of uræmia remains unknown.

Symptoms.—Symptoms Referable to the Nervous System.—*Convulsions.*—These, of greater or less severity, are among the commonest and most conspicuous of the symptoms of uræmia. They vary in degree from mere twitchings of muscles to fully developed epileptiform attacks. The latter bear a very close resemblance to true epileptic seizures, and present the ordinary sequence of tonic and clonic convulsive movements, followed often by a longer or shorter period of unconsciousness. Only by the antecedent symptoms, or by the evidences of renal disease, may it be possible to distinguish the condition from epilepsy.

The onset may follow upon a period of chronic uræmia, with headache, vomiting, and perhaps dimness of vision, of which the convulsion is merely the culmination. On the other hand, the antecedent symptoms may be very slight, such as headache of no severity, with or without nausea; or, again, the convulsions may set in with stormy suddenness, in patients who are not conscious of any impairment of health sufficient to lead them to seek for medical advice, as is the case with not a few of the sufferers from granular kidney.

Occasionally, some subjective sensation or involuntary movement, such as is included among the recognized auræ of true epilepsy, precedes the convulsive seizure. Not infrequently the convulsions begin locally, as, for example, in the muscles of the face or of one limb, and they are usually more pronounced in one-half of the body. As in epilepsy an initial tonic stage, during which the embarrassment of respiration may cause pronounced cyanosis and turgidity of veins, following upon a stage of pallor, is succeeded by a clonic stage, during which the tongue may be bitten.

During the fit, the pulse, which was previously of high tension in the majority of cases, may become small, rapid, and easily compressible; however, it sometimes happens that the tension is maintained throughout. The pupils are usually dilated and active, but they are in some instances contracted. Sir William Gowers states that nystagmus is sometimes observed, and lays special stress upon the implication of the facial muscles in uræmic convulsions. The temperature is usually raised during the convulsive period, but this, like every other rule relating to uræmia, is by no means absolute, and the record may be conspicuously subnormal. The fit may be followed by a period of somnolence, as in epilepsy, or consciousness may not be recovered, the patient remaining in a state of coma, or, again, on recovery he may prove to be temporarily blind. The convulsions may follow each other at considerable intervals, or may recur so quickly that the patient's condition may be described as one of *status epilepticus*. Death may occur during a convulsion, and, as has already been mentioned, the first convulsion may prove fatal.

Certain subvarieties of uræmic convulsions must be referred to. Thus, in

rare instances the spasm is limited to one-half of the body, or even to a single limb. Jaccoud[1] has described a tetanic variety, in which the clonic stage is altogether absent, whilst the tonic spasm may be localized to a group of muscles, such as those of the neck, or may be so generalized as to give rise to opisthotonos. Instead of relaxing in the course of a few minutes, such tonic spasm may persist to the agonal stage, and only then be relaxed. The writer has seen such tonic rigidity of the limbs with rigidity of the neck and retraction of the head in children suffering from uræmia, both as a sequel of convulsions and apart from fits.

Yet another subvariety is the ataxic one, described by Rilliet and Barthez,[2] in which irregular movements of the limbs persist for hours instead of for the short period usually covered by an ordinary uræmic convulsion, and are not preceded by any tonic stage. Ascoli considers that these movements are better described as choreiform than as ataxic.

Paralyses.—That local paralyses, usually of hemiplegic distribution, may occur in uræmic conditions, in cases in which no gross cerebral lesions can be found postmortem other than œdema of the brain and its membranes, may be regarded as an established fact. Chantemesse and Tenneson,[3] who have described such cases, consider that the symptoms are due, in all probability, to a circulatory disturbance, which is evidenced by œdema and cerebral congestion. Such paralyses have occasionally followed upon unilateral convulsions, but in some instances their onset has not been preceded by any epileptiform seizure, at any rate of a conspicuous kind. In some cases there has been right hemiplegia with aphasia, and aphasia has also been met with apart from any paralysis of limbs, as in cases recorded by Lancereaux[4] and by Rose.[5] Rose's patient, who was a man aged thirty-two years, developed aphasia so complete that "yes" and "no" were the only words which he could utter. Half an hour after the onset of the aphasia tonic spasm and clonic movements of the limbs occurred, with dilated and inactive pupils. Other kinds of paralyses have also been described, such as monoplegia, ocular paralyses, and, in a case of Senator's, bulbar symptoms. Hemianæsthesia has occasionally been observed in association with hemiplegia.

The duration of the paralytic symptoms varies greatly in different cases. Thus, in a case described by Boinet, two convulsive attacks, limited to the right half of the body, were followed, after a few hours, by transitory right hemiplegia and hemi-anæsthesia, which lasted not longer than twenty minutes. On the next day a second paralytic attack of four hours' duration occurred, and again on the third day coma developed with paralysis lasting for three hours. In spite of these grave events, the after progress of the case was favorable and no further paralyses occurred. In another group of cases the paralytic seizures have preceded death by a day or two only, and in a case reported by Tenneson the paralysis persisted until the death of the patient, which occurred a fortnight after its onset.

Disorders of the Special Senses.—Sensory disturbances, and especially disorders of vision, are among the most noteworthy and remarkable of the

[1] *Leçons de Clin. Méd.*, Paris, 1867, p. 734.
[2] *Traité Clin. et Prat. des Maladies des Enfants*, Paris, 1854.
[3] *Revue de Médecine*, 1885, v, 935.
[4] *Union Méd.*, 1887, 3d ser., xliii, 413, 665, 705.
[5] *Berliner klin. Wochenschr.*, 1898, xxxv, 193.

symptoms of uræmia. Doubtless, in some instances, impairment of vision is a result of albuminuric retinitis and of optic neuritis, but it is a well-recognized fact that such lesions may exist, even in very pronounced forms, apart from any conspicuous failure of sight, and it is no less certain that complete amaurosis develops in association with uræmic symptoms, apart from any changes in the fundus of the eye which can be detected with the ophthalmoscope. Moreover, the sudden onset and transient character of the amaurosis is hardly compatible with the presence of an organic lesion.

Actual blindness may be preceded by a period of dimness of vision, or the stage of dimness may be at no time overstepped. Not infrequently the patient emerges from a convulsive attack completely amaurotic and unable to perceive even a bright light, or, again, the blindness may be, at least for a time, an isolated symptom of the uræmic state. The loss of vision may last for a few hours or even less, or for a few days. In some, and especially in puerperal cases, a more lasting blindness develops, which suggests that permanent damage has resulted from the lesion to which the amaurosis is due.

As the sight is restored recovery is not always uniform over the field of vision, and large areas of blindness may persist for a time after other parts of the field have regained their function. Even persistent hemianopsia may be left, and in a case of this kind, which was recorded by Pick,[1] a patch of softening was found, after death, in the cortex of the occipital lobe. Pick looked upon this as affording evidence that such hemianopsia results from a definite cortical lesion, brought about by circulatory disturbance and possibly by thrombosis.

In uræmic amaurosis the pupils usually, but not invariably, retain their activity. This so frequent activity of the pupils suggests that the lesion, whether its origin be vascular or toxic, lies behind the corpora quadrigemina and is probably cortical, and is opposed to the alternative explanation which ascribes the blindness to œdema of the retina or of the optic nerve. A central area of blindness for blue and yellow has been observed after recovery from uræmic amaurosis, but, as König pointed out, and as C. Gerhardt[2] has also shown, central blue blindness is sometimes present in cases of granular kidney apart from any characteristic uræmic symptoms, usually in association with albuminuric retinitis but also in cases in which there is little amiss detected with the ophthalmoscope. It would seem to be a renal rather than a uræmic symptom. The affections of the sense of hearing met with in uræmia are of several different kinds. Singing in the ears and noises of various kinds are comparatively common. Partial deafness is less common and complete deafness is decidedly rare. Tinnitus may be accompanied by partial deafness, or impairment of hearing may be present, apart from tinnitus. Dieulafoy[3] describes severe pain in the ears and face as an occasional accompaniment of impairment of hearing, but in some of the cases which he quotes definite aural lesions were present, such as perforation of the tympanic membrane, or injection along the handle of the malleus.

Coma, Delirium, and Mania.—Drowsiness, apathy, and coma are conspicuous among uræmic symptoms. The onset of coma is often gradual in

[1] *Deutsch. Arch. f. klin. Med.*, 1905, lvi, 69.
[2] *Münchener med. Wochenschr.*, 1900, xlvii, 1.
[3] *Gazette Hebdom.*, 1878, xv, 49.

chronic cases. It may be preceded by mental slowness or drowsiness lasting for weeks, and in favorable cases this stage may never be overstepped, restored functional activity of the kidneys being attended by a corresponding improvement of the mental state. On the other hand, it not infrequently happens that a convulsion of sudden onset leaves the patient in a deeply comatose condition.

The unconscious patient may exhibit twitching of the limbs, or convulsive attacks may occur at intervals. The breathing may be stertorous, or may have the peculiar whiffing character upon which Addison laid special stress. Sometimes it assumes the Cheyne-Stokes rhythm. In some cases the cerebral disturbance assumes a more active form, and a muttering delirium may persist for days with incoherence of words and ideas. As Senator points out, such delirium is most often seen in adult patients who are sufferers from chronic renal troubles. Delirium, which may be of all degrees of activity up to actual mania, may be an early symptom of uræmia, and may replace coma as the sequel of a convulsive attack.

Occasionally the patient exhibits delusions of persecution and endeavors to leave his bed and to escape from his imaginary persecutors. In other instances the mental derangement assumes a melancholic form, in others, again, it has a religious or erotic character, or there may be acute and violent maniacal outbreaks. The duration of such symptoms, which have been well described and grouped by Dieulafoy, is very variable and in chronic cases they may persist for weeks or months.

Headache and Giddiness.—Headache is one of the commonest symptoms, and in chronic cases it is often the earliest of all. The headache has no constant character. In distribution it may be frontal, occipital, or general, and it sometimes has the unilateral distribution which is associated with migraine. It may be slight or of great severity. Giddiness, also, is a common early symptom, and in association with headache it may give the first warning of approaching danger in cases of granular kidney. It must not be forgotten, on the other hand, that sufferers from granular kidney often experience a form of giddiness which appears to be directly associated with the high arterial tension which is so important a feature of the disease.

State of the Pupils.—This varies so greatly in different cases, and even in the same case at different periods, that it is of comparatively slight diagnostic value. In acute attacks the pupils tend to be dilated, but may be of normal size. In chronic uræmia myosis is, on the other hand, by no means uncommon. It has already been mentioned that during a period of amaurosis the pupils usually retain their activity.

Symptoms Referable to the Alimentary Tract.—Scarcely inferior in clinical importance to the disturbances of the nervous system are those referable to the alimentary canal. These are seldom wholly absent, and in some cases dominate the clinical picture. *Loss of appetite* and *nausea* are usually complained of, and vomiting is a common symptom, especially in cases of the more chronic kind, in which headache and vomiting usually precede and usher in the more alarming manifestations, and are often the sole evidences of uræmia over considerable periods. The *vomitus* may contain partially digested or undigested food, but is often liquid and may be stained green by biliverdin.

It is probable that uræmic vomiting, although it is usually preceded

by nausea, is often of cerebral origin, but Lancereaux[1] and others are inclined to attribute an important share in its causation to the excretion of urea into the alimentary canal, and its conversion therein to ammonium carbonate. Violent and persistent hiccough is of very evil omen, and usually precedes a fatal ending by a few days only. In some cases such hiccough is the earliest and most conspicuous uræmic symptom in chronic renal disease, and perhaps most often in cases of granular kidney. Diarrhœa, although decidedly less common than vomiting, usually appears in the last stages of chronic renal diseases. The stools exhibit no constant character. They contain urea and ammonium carbonate, may be watery or rich in mucus, and may contain material resembling frog's spawn. They are sometimes tinged with blood. Such functional disturbances as these are not necessarily associated with any gross changes in the gastric and intestinal walls, although these may exhibit evidences of catarrh, and in dropsical cases the alimentary mucous membranes may be œdematous. However, certain definite lesions, which are usually spoken of as uræmic, are occasionally found postmortem, or seen during life.

Of such lesions the so-called *uræmic stomatitis* calls first for mention. It has been specially studied by Lancereaux, Hirtz,[2] and especially by Barié,[3] who has published a monograph upon the subject. Barié distinguishes two varieties of such stomatitis; an erythematopultaceous and an ulcerative. In the first mentioned form there is at first merely injection and some swelling of the buccal mucous membrane; later, the tongue becomes coated with a grayish tenacious coating, of consistence like glue and of a sickly odor, and the gums and mucous membrane of the buccal cavity acquire a similar pultaceous covering. Beneath this coating the mucous membrane is dry and deeply injected, but is not ulcerated. When the sticky coating is removed it soon reforms. The saliva becomes scanty and tenacious, appetite is lost, and there is a loathing of food. Vomiting usually occurs and sometimes diarrhœa also.

In the second or ulcerative variety, which is far less common, the symptoms at first resemble those of the pultaceous stomatitis, but after a few days ulcers develop upon the gums and buccal surface of the lips and cheeks. These are of various shapes, and may be few or many. They are small, seldom exceeding 0.5 cm. in diameter, and of various depths, but often very shallow. In the centre of the ulcer there is often a caseous patch surrounded by a deeply injected zone. With the development of the ulcers the saliva, which has previously been scanty and tenacious, becomes very abundant and may amount to as much as 800 to 900 cc. in the twenty-four hours. In either form of stomatitis there may be a subjective sensation of heat in the mouth, but this is specially prominent in the ulcerative cases.

Hemorrhagic erosions of the stomach have been described by Pineau and by Lancereaux. In a case recorded by Matthieu and Roux[4] there was extensive ulceration of the stomach and also of the intestine. A large ulcer near the pylorus had the appearance of an ordinary gastric ulcer, whereas the others were merely superficial and much more extensive. *Ulceration of the intestines*, although rare, has been met with in a sufficient number of

[1] *Union Médicale*, 1887, 3d ser., xliii, 329.
[2] *Semaine Méd.*, 1902, xxii, 109.
[3] *Archiv. gén. de Méd.*, 1889, clxiv, 415, 690.
[4] *Ibid.*, 1902, clxxxix, 14.

cases to justify its inclusion among uræmic, or perhaps to speak more accurately, among renal accidents.

The colon, cæcum, and lower portion of the ileum are the usual seats of such ulceration. The ulcers are generally multiple and are for the most part located away from the mesenteric insertion. In some instances they appear to have originated in Peyer's patches or in the solitary follicles, but not in all cases. They may be oval in shape, or may have irregular and map-like outlines. Their borders are clean cut, not heaped up and not undermined. The floors of the ulcers may be formed by the submucosa, by the muscular coat or the peritoneum, and perforation is not an uncommon accident. The floors may be smooth and clean, or covered by a necrotic slough, or again by inflammatory exudate. Between the ulcers the mucous membrane may be injected, and it is apt to be pigmented. Healed ulcers have sometimes been found in addition to recent ones. In the case described by Matthieu and Roux, which has already been referred to, there was a chain of ulcers, confluent and covered with a diphtheroid exudate, extending upward from just above the ileocæcal valve for a distance of some 75 cm.

Symptoms Referable to the Circulatory System.—It is probable that the cardiovascular changes, which constitute so prominent a feature in chronic renal diseases, have their origin in the presence of noxious materials in the circulating blood, and are themselves, in a sense, of uræmic origin. There need be little hesitation in asserting that high arterial tension is a natural outcome of uræmic poisoning. On the other hand, it is equally certain that high pulse tension is no constant feature of the condition, and may be wholly wanting in the uræmic state. The wide differences observed in the degree of arterial tension in undoubted cases of uræmia are apparently due to the conflict of two factors, and it would seem that, in addition to the influence of the loaded condition of the blood in raising arterial tension, the enfeeblement of the heart, which is so often present, has a contrary influence which needs to be taken into account. Accordingly, as one or other of these factors preponderates, so will the tension of the pulse be high, low, or intermediate in degree. If this be the true explanation of the clinical findings, it will be obvious that, given a condition of uræmia, the absence of conspicuously high tension must be looked upon as a by no means favorable sign.

The occurrence of *cardiac failure* in cases of renal disease is a sufficiently common phenomenon, and, in addition to the mechanical strain to which the heart is subjected in its endeavor to overcome peripheral obstruction, degeneration of its muscular walls plays no unimportant part in bringing about such failure. Indeed, experience in the postmortem room teaches that a large proportion of sudden deaths among persons over forty years of age are due to myocardial degeneration in association with granular kidneys. The rate of the *pulse* also exhibits marked differences. Before the attack, and even during it, the pulse may be slow and irregular, but during the convulsive seizures it is more commonly small, soft, and rapid.

The occurrence of *pericarditis* as a terminal symptom in renal cases, and especially in cases of granular kidney, has long been known, and was observed by Bright. Such pericarditis is usually revealed by the development of a loud friction sound, but, as it is generally unaccompanied by any precordial pain, or by other symptoms which direct attention to the heart, it may easily be overlooked. The mode of its occurrence is suggestive of a terminal infection, but bacteriological investigations have hitherto lent no support to

this interpretation. Thus Banti[1] failed to detect any bacteria in the lymph in two cases of renal or uræmic pericarditis, and inoculation of animals was followed by no results. Becco also failed to obtain any organisms from the pericardium in a case which he examined, but other organs bore witness to infection by the colon bacillus. Becco observed pericarditis in rabbits after ligature of the ureters, an observation which seems to lend support to the alternative view that the inflammation of the pericardium has a toxic origin.

Symptoms Referable to the Respiratory System.—*Dyspnœa* is a common symptom, but a study of the cases in which it is present shows that it may arise from several distinct causes. Often the respiratory disturbance is rather to be classed as renal or cardiac than as uræmic, and in chronic renal diseases there are several factors at work which may induce it.

The dyspnœa may be of pulmonary origin and due to emphysema, which is, in some degree, an almost constant concomitant of granular kidneys, and is occasionally so pronounced as to dominate the clinical picture. In other cases the dyspnœa is due to a complicating bronchitis, and in others, again, results from cardiac failure, as is evidenced by the state of the pulse and the presence of other signs of such failure. Again, an urgent form, met with in renal cases, may result from pulmonary œdema, and is attended by profuse, frothy expectoration, which is apt to be blood-stained. This, again, although a renal rather than a uræmic event, is not uncommonly met with in association with more strictly uræmic phenomena. Pneumonia, hydrothorax, and hydropericardium must also be mentioned as causes of dyspnœa in renal cases, and the rarer œdema of the larynx which naturally occasions urgent respiratory distress.

To a different category from those so far mentioned belongs the condition known as uræmic asthma, which occurs in a paroxysmal manner; in this as in ordinary asthma, the dyspnœa is mainly expiratory. No physical signs are to be detected apart from stridor. Such uræmic asthma is apt to supervene in the later stages of chronic renal disease, and in cases of granular kidney may be of sudden onset; it is not necessarily preceded by any serious indications of impairment of health.

The following brief record of such a paroxysm will serve to illustrate the main features of uræmic or renal asthma: A man, aged sixty-two years, who had experienced many attacks of articular gout, and exhibited signs of granular kidneys, including cardiovascular changes and albuminuria, travelled to town one morning in his usual health, save that he had some headache. At 5.30 P.M. he noticed that his breath was short, and the dyspnœa increased rapidly. When seen at 7.15 P.M. he was sitting upon the side of his bed, leaning forward, with pronounced cyanosis and respiratory stridor. The dyspnœa was mainly expiratory. His lungs yielded, everywhere, a tympanitic note on percussion, and the cardiac dulness was overlapped. Air entered freely to the bases of the lungs, and no moist rales were heard. There was no expectoration and, indeed, no cough. The skin was covered with a cold sweat, and there was marked coldness of the extremities. The patient complained of some epigastric pain. The respirations were 40 to the minute. The pulse rate was 84, the arterial tension was very high, and the radial artery felt like a wire.

[1] *Centralbl. f. allgem. Pathol. und pathol. Anatomie*, 1894, v, 461.

Various measures were adopted for his relief, but, as the patient afterward stated, the inhalation of oxygen was alone helpful. From 8.30 P.M. onward his condition gradually improved, and after 9.30 the improvement was rapid. Warmth returned to the extremities, the pulse tension was notably diminished, and the breathing became much easier. By 10.30 P.M. he was fairly comfortable, and next morning his pulse remained much softer, and he was expectorating a small quantity of frothy mucus of a rusty tint. Some moist sounds were then audible at the bases of both lungs. The temperature was not raised during or after the attack.

The great increase of pulse tension, which was so marked a feature of the above case, is characteristic of uræmic asthma, and at once serves to distinguish the condition from other varieties of dyspnœa met with in the uræmic state. This point is very clearly brought out by M. Weiss,[1] in his admirable description based upon a series of cases. In some instances the vasomotor storm is preceded by a stage of vascular relaxation with a resulting peripheral hyperæmia, but upon this the stage of spasm quickly supervenes. Weiss suggests that the blood, loaded with extractives, irritates the vasomotor centre, and causes vascular spasm, and attributes the dyspnœa to a resulting anæmia of the respiratory centre.

Among the respiratory symptoms, periodic breathing of the Cheyne-Stokes variety claims a place—a form of dyspnœa which is due to an impaired response of the respiratory centre to the call for oxygen. This explanation has been shown to be almost certainly the correct one by the recent investigations of Pembrey and his coadjutors, who have shown that an increase of carbon dioxide and an increase of oxygen in the inspired air alike serve to abolish the peculiar rhythm; the former by keeping the centre continuously stimulated up to the required degree, the latter by removing the necessity for the series of deep respirations, and for the period of apnœa which follows excessive aëration.

The occurrence of Cheyne-Stokes breathing in uræmia is by some attributed to cardiac failure, which is certainly one of the more common causes of such dyspnœa. However, there are difficulties in the way of accepting this explanation without qualification, and it is at least possible that, when developed as an early symptom of uræmia, the sluggish response of the respiratory centre may have a toxic origin.

Temperature.—In chronic uræmia the body temperature tends to be subnormal. In some instances the fall is very conspicuous and subnormal readings are often continuously observed. On the other hand, febrile disturbance is usually present in association with acute attacks, and this, apart from any obvious complications, such as pneumonia or pericarditis. The fever may even attain to hyperpyrexia. Strümpell, who attaches considerable prognostic importance to the state of the body temperature, regards exceptionally high or exceptionally low readings as of very unfavorable significance, whereas the outlook is decidedly better when the temperature does not depart very widely from the normal in either direction. This opinion is borne out by experience.

Cutaneous Lesions.—*Itching*, which may be intense, is a not uncommon symptom in uræmia, and, owing to the presence of urea in the sweat, the skin may be covered with a crystalline efflorescence of that material. With

[1] *Zeitschr. f. Heilkunde*, 1881, ii, 79.

these exceptions, skin affections must be classed among the rarer manifestations. However, there are strong reasons for including a form of erythematous eruption among the symptoms, for it has repeatedly been observed as a precursor of the more usual manifestations, or in association with these, in cases which have shortly afterward ended fatally. Such an eruption was first described in 1870 by Huet, who gave it the name of erythema papulatum uræmicum, and it has since been described by Bruzelius, Le Cronier Lancaster,[1] and others. Lancaster describes the rash as first appearing in discrete maculæ of a bright-red color—usually upon the extensor surfaces of the hands, forearms, and legs. These quickly become papular, and fresh maculæ and papules appear on all parts, including the face, palms, and soles. The mucous membranes are also affected and the throat becomes sore and congested. The papules tend to become confluent over large areas, especially on the back, arms, and thighs. After the lapse of three or four days the eruption may subside, and extensive and free desquamation may follow, leaving the skin of a dull-red tint and brawny, whilst some of the papules may become hemorrhagic. Sometimes the rash assumes an eczematous character, with the formation of scabs and crusts, and pustulation may occur. As a rule, itching is a prominent symptom. The prognostic significance of the erythema is decidedly evil, and death usually follows within a few weeks of its appearance.

H. Thursfield[2] has collected records of various skin eruptions occurring in association with renal disease and uræmia, among which are those of a few examples of urticaria and bullous eruptions, and of a series of cases of general desquamative dermatitis. However, it would seem that if any variety of rash is rightly classed as uræmic it is the papular eruption described above; but of this eruption Thursfield could only find descriptions of 46 cases.

The Symptoms which Result from Anuria.—Whereas lesions of both kidneys which bring about conspicuous impairment of their functions usually result, sooner or later, in the development of uræmia, it is a very remarkable fact that, when the excretory functions of both kidneys are completely suspended, the symptoms observed are not those of ordinary uræmia, and are comparatively slight, although, if the anuria persist, a fatal ending is, after no long interval, inevitable. The cases in which such a condition is most often observed are those in which, one kidney having been previously rendered useless owing to obstruction of its ureter, a calculus lodges in the ureter of the remaining kidney. Less frequently both ureters are simultaneously obstructed by calculi or involved in a new-growth. However, a similar result is brought about by thrombosis of both renal arteries, as in cases described by Rose Bradford and by Herringham and Griffith.

In a large proportion of cases of obstructive suppression some urine is passed at times, presumably because the pressure behind the obstacle reaches a level at which some of it is able to pass. Such urine is very pale, of low specific gravity, and contains little urea or other excretory products. It is sometimes blood-stained. The occasional passage of urine having the above characters affords little relief and does not long postpone the end. Obstructive suppression, unless it be relieved by the passage of a calculus or by surgical procedures, is necessarily fatal, but as many as seven or eight

[1] *Clinical Society's Transactions*, London, 1892, xxv, 49.
[2] *Medico-Chirurgical Transactions*, London, 1900, lxxxiii, 221.

days may elapse before conspicuous symptoms develop. Although life may be prolonged for three weeks, death commonly supervenes in from nine to eleven days from the onset.

During the earlier days the patient may exhibit hardly any symptoms suggestive of grave illness. Sleeplessness and gastric disturbance are usually present, but there may be no headache or vomiting. Progressive muscular weakness is common; the mind usually remains clear. Of the symptoms of the later days, dryness of the mouth and tongue, contraction of the pupils, and muscular twitching are among the most prominent and most constant. Convulsions are absent. The patient may become more and more drowsy and there may be some delirium, but coma is rare, and in not a few cases the patient remains fully conscious up to the moment of death. The appetite may be maintained up to within a few days of the end, but at the last usually fails completely. Curiously enough, the ammoniacal urinous odor which is so commonly noticed in uræmia is wanting in cases of obstructive suppression. The breathing is slow and difficult, a symptom which Sir William Roberts attributed to weakness of the respiratory muscles. The pulse rate is little affected or is slightly quickened toward the end; the temperature tends to fall below the normal level during the later days.

The Classification of Uræmic Attacks.—Attacks of uræmia may be classified according to their most prominent symptoms, as nervous, alimentary, or respiratory, and so much is some special class of symptoms wont to preponderate in individual cases that a classification upon such lines seldom presents any difficulty More commonly the cases are grouped as acute, chronic, or latent, and the subdivision of the acute cases into acute and fulminating, suggested by Rose Bradford, has a sound clinical basis.

Fulminating uræmia most commonly occurs in the course of chronic renal diseases. A patient with granular kidneys, who may not be conscious of any serious impairment of health, is suddenly attacked with uræmic convulsions which may even prove fatal in the course of a few minutes, or by urgent uræmic asthma; or, again, a sufferer from that form of nephritis which is associated with contracted white kidneys develops acute uræmic symptoms with little previous warning. In the acute form which may develop in cases of acute nephritis, and is also occasionally seen after operations upon the lower urinary tract, such as dilatation of a stricture, convulsions may occur after a short premonitory period in which headache, vomiting, dyspnœa, or delirium are the most prominent manifestations.

Chronic uræmia is best seen in cases of chronic parenchymatous nephritis, in which the minor symptoms of the condition, such as nausea, vomiting, and sometimes diarrhœa, may precede by a considerable period the onset of graver manifestations, and may persist from day to day for weeks at a time.

The name latent uræmia is applied to the condition met with in cases of obstructive anuria, in which the more characteristic uræmic symptoms may be absent up to the fatal ending.

Diagnosis.—The diagnosis of uræmia presents difficulties in not a few cases. Thus, when a patient is seen for the first time in a condition of coma, other varieties of coma have to be excluded. This is done by consideration of the state of the patient and by the history of his illness. The state of the pupils, as to equality, dilatation, or contraction, the odor of the breath, the presence or absence of albumin to the urine, the tension of the pulse and state of the arteries, and the presence or absence of evidences of paralysis of limbs, all need to be taken into account in arriving at a diagnosis. The

history of a convulsion at the onset is very important, but it must not be forgotten that a series of convulsions followed by prolonged unconsciousness may occur in epilepsy and in the course of general paralysis of the insane, and that albuminuria may follow convulsive attacks. Difficulties of another kind may arise from the protean nature of the attacks, and the prominence of some particular symptom which may be one of the less common ones. Thus, in one case vomiting may be almost the only symptom, in another hiccough. An attack may be ushered in by delirium which may even be maniacal, and Cheyne-Stokes breathing may be the earliest symptom. Hence, it comes about that when any symptom of the uræmic group is met with in patients suffering from renal disease, its uræmic origin is to be suspected.

Prognosis.—This is always grave, and in connection with it two main points have to be considered, namely, the chance of recovery from the actual attack, and the likelihood of a recurrence of uræmia at an early date.

In acute nephritis with almost complete suppression of urine the patient may die during an attack of acute anuria, but, on the other hand, a patient who has exhibited grave uræmic symptoms, such as convulsions followed by coma and amaurosis, may nevertheless make a complete recovery, the danger of recurrence being wholly averted. On the other hand, in cases of chronic nephritis, even though the danger be averted for a time, a recurrence is highly probable, or, indeed, almost inevitable, at no very distant date, and in the great majority of cases the attack, if not at once fatal, marks the commencement of a rapid downward progress. The immediate prognosis of the attack depends in part upon the violence of the symptoms, for the fulminating attacks are usually fatal, and in part upon the response to our efforts to improve the working of the kidneys and to eliminate the poison by other paths. In latent uræmia a fatal ending is inevitable unless it is possible, by surgical procedures or otherwise, to restore the functional activity of the kidneys.

Treatment.—The methods of treatment which have met with general acceptance are, for the most part, based upon the assumption that the poison at work is a nitrogenous product which fails to be adequately excreted by the diseased kidneys. Thus, the attempt is made, by restrictions of diet, to limit the formation of the end products of protein catabolism, and at the same time to reduce the accumulation of such products in the blood by venesection, and by encouraging their vicarious elimination by other channels than the kidneys.

Many patients who develop uræmia are already under treatment on account of the primary renal disease, and appropriate treatment of the nephritis offers the best chance of averting the onset of uræmia. In cases of acute nephritis in which the output of urine is scanty, as also in cases of parenchymatous nephritis in which headache and vomiting or other symptoms of incipient uræmia are beginning to manifest themselves, the application of dry cups to the loins will often prove of much service, and is usually followed by a conspicuously increased output of urine.

Copious diaphoresis is an important and well-established method of treatment. It has been objected that the quantity of excretory products, as measured by urea, which can be thus vicariously removed, is comparatively small, and that profuse sweating will tend to increase their concentration in the blood. However, clinical experience teaches us that hot baths, and hot air or vapor baths, have a decidedly beneficial effect in uræmic cases, and the pathology of the conditions is still so obscure that it would be very

unwise to abandon a plan of treatment of proved utility on merely theoretical grounds.

In acute cases, in which a prompt and copious diaphoresis is aimed at, the subcutaneous injection of nitrate of pilocarpine in doses of $\frac{1}{6}$ grain (gm. 0.01) may be resorted to, but is now always regarded with less favor than formerly. In connection with diaphoresis, as with other plans of treatment, the condition of the individual patient needs to be carefully considered, and especially the state of the heart and character of the pulse. The pulse should be carefully watched during the administration of the sweat bath, and stimulants should be given if necessary.

Hydragogue cathartics are of undoubted service. In the more chronic cases saline purgatives or compound jalap powder, aided, if necessary, by enemata, will usually suffice, but in acute attacks more drastic cathartics, of which elaterium is most in favor, are called for. The utility of purgation in uræmia is probably only in small part due to the comparatively scanty elimination of waste products by way of the bowel. Vomiting, which is so common a symptom, aids the vicarious elimination, and lavage of the stomach has been recommended with the same object in view. Venesection, with the withdrawal of 12 to 20 ounces of blood, proves of great service in not a few cases, and is regarded by some physicians as by far the most important of all the therapeutic measures employed in uræmia. Whether or not bleeding should be resorted to will be largely determined by the state of the pulse, and when a pulse of conspicuously high tension is a prominent feature, venesection will commend itself, rather than in cases in which a soft and feeble pulse affords evidence of a failing heart. The benefit which results from bleeding is thought to be largely attributable to the withdrawal of a portion of the toxic material in the shed blood. Infusion of normal saline solution to replace the blood withdrawn is frequently practised, and in cases in which œdema is absent, as in acute uræmia in connection with granular kidneys, saline infusions, apart from venesection, have been recommended.

Removal of cerebrospinal fluid by lumbar puncture has recently been employed with benefit in the treatment of uræmic conditions.

For the reduction of excessive pulse tension, nitroglycerin, or in acute attacks the inhalation of nitrite of amyl, may be employed; but even in uræmic asthma, in which high tension plays so conspicuous a part, these drugs may afford but little relief. Digitalis is often of service in chronic cases, both in virtue of its action as a cardiac tonic and as a diuretic. Inhalation of oxygen, and especially its continuous inhalation, is of very real service in the treatment of uræmic asthma, and is strongly recommended by Samuel West as calming the distressing restlessness which is a prominent symptom in many uræmic cases, and even as modifying convulsive attacks.

For the control of convulsions inhalation of chloroform is usually very effectual, and chloral and bromides may be administered either by the mouth or per rectum. Morphine, the use of which has been strongly recommended by Stephen Mackenzie, Osler, and others, often proves most valuable in the treatment of uræmic states, and its judicious use has been shown to be unattended by the dangers which were formerly regarded as contra-indicating its employment. In renal asthma it is said to afford more relief than any other therapeutic agent, and it also gives relief from restlessness, insomnia, and such conditions as the mental disturbances and Cheyne-Stokes dyspnœa which usher in the onset of uræmia in some cases of granular kidney.

CHAPTER V.

NEPHRITIS: INTRODUCTION AND ETIOLOGY.

By JAMES B. HERRICK, M.D.

Introduction.—By the term nephritis is meant an inflammation of the kidney, and, as it is commonly employed, a non-suppurative inflammation is implied. If other than the non-suppurative form is meant, a qualifying adjective, as "suppurative," "pyelo," etc., is prefixed. Non-suppurative nephritis is often spoken of as Bright's disease, or morbus Brightii, the terms nephritis and Bright's disease being used interchangeably. Strictly speaking this is not correct. Bright described those inflammations of the kidney accompanied by albuminuria and dropsy, so that his description did not include the group of nephritides in which there is no dropsy. It would seem, however, as though little is to be gained by quibbling over the question as to whether a given case is one of acute nephritis or acute Bright's disease, or whether it is acute nephritis and also acute Bright's disease. Cannot the name "Bright's disease" be used as a "convenient and non-prejudicial expression," and in a sense that is admittedly broad and made to cover all the non-suppurative inflammations and many of the degenerative processes of the kidney, even though Bright failed to include the non-dropsical forms of nephritis, so that historically the term is a misnomer? To attempt to draw fine distinctions between the terms nephritis and Bright's disease without some better substitute tends rather to complicate than to simplify matters. So, too, in reality, it is not correct to speak of some of the diseased conditions commonly spoken of as nephritis as inflammations of the kidney, *i. e.*, as exudative and proliferative in character. The granular atrophy, for example, is, in the strict sense, not an inflammation. But until clinical and pathological differentiation is more sharply defined, the term nephritis, or Bright's disease, may conveniently be employed to designate the non-suppurative inflammations of the kidney, it being tacitly understood that some forms of "nephritis" are degenerative or atrophic in character rather than inflammatory, and that some conditions called Bright's disease are different from anything actually described by Bright.

There is a quite general agreement as to the division of all cases of nephritis into the two classes of the acute and chronic. Clinically, the distinction between acute and chronic must rest not so much on the duration of the disease or its possible outcome in recovery, as on the abruptness of its onset and the severity of the symptoms. That suddenly developing symptoms may nevertheless be slight and pass unobserved is well known, so that often great practical difficulty is met with in attempting accurately to decide as to the acute character of a nephritis from its clinical history; and the anatomical distinction is also often far from easy. Subdivisions of the *acute* class into varieties are occasionally attempted, sometimes on an

etiological basis, *e. g.*, malarial nephritis, or sometimes on a histological basis, *e. g.*, glomerular or tubular nephritis. Most writers are content, however, with describing an acute nephritis and pointing out certain features which clinically or pathologically distinguish acute nephritis as it is due to different causes, *e. g.*, scarlatinal nephritis or the nephritis of cholera, the nephritis of pregnancy or of carbolic acid poisoning, etc. The subdivision, then, of the acute nephritis into a large number of varieties is seldom made, although greatly to be desired as soon as an etiological classification becomes possible.

No serious, at least no successful, attempt has ever been made to classify cases of *chronic nephritis* from the standpoint of etiology. Morbid anatomists and pathologists are far from unanimous in their descriptions of the various types or groups of this disease. And physicians are not always able to make a differentiation that is satisfactory from the clinical point of view or that holds good in the light of postmortem revelations. Yet it is important that we have some working classification, even though it be somewhat faulty and largely artificial.

From the time of Bright (1827) down to the present there has been more or less confusion of ideas concerning chronic nephritis. Rayer, a few years after Bright's first paper, made four varieties of chronic nephritis. In 1867 Rindfleisch declared that "the pathological anatomy of the kidney is certainly the subject which has stimulated the most investigation, and yet to-day it is the least complete chapter of the whole work." And Bartels,[1] a little later, besides quoting with approbation the sentence from Rindfleisch, adds that "it is apparent that the doctrine of the diffuse renal diseases cannot be regarded as settled from any point of view." Senator,[2] writing in 1901, says: "There is at present no detailed classification that has met with general approval and acceptance." Bradford[3] (1901) says: "Chronic Bright's disease, however, is the form in which the greatest diversity of opinion, as to its nature and forms, exists."

At the meeting of the German Pathological Society in 1905 there was a general discussion of morbus Brightii. Ponfick,[4] in a leading paper, emphasized the importance of further careful correlated clinical and anatomical study of cases, so that more order might be brought out of the present confusion. Friedrich Müller,[5] in an inspiring and masterly critique of recent views concerning Bright's disease, admitted the unsatisfactory nature of our knowledge concerning the true character of the lesions in the kidney, our loose methods of classification, the difficulties to be overcome before an exact etiological classification is possible, and our use of a nomenclature that is neither historically, clinically, nor anatomically correct. He even proposed the use of a new term, "nephrosis," to include in a comprehensive way the degenerative lesions of the kidney that could not, strictly speaking, be called "nephritis."

Yet from out the confusion some semblance of order appears and certain facts stand forth that permit of arrangement into a working classification.

[1] *Ziemssen's Encyclopædia*, American edition, xv, 187.
[2] *Die Erkrankungen der Nieren*, Zweite Auflage, Berlin, 1902, p. 194.
[3] Diseases of the Kidneys in *Gibson's Practice of Medicine*, 1901, ii, 316.
[4] *Verhandl. der Deutsch. path. Gesells. Centrabl. f. allg. Path. und path. Anat.*, 1906, Band xvi, 49–64.
[5] *Ibid.*, pp. 64–99.

First, it may be stated that the *kidney of congestion* is, by common consent, ruled out of the category of the nephritides and Bright's disease. Traube made it clear that it was not an inflammation. Rokitansky, Traube, Virchow, and others likewise excluded *amyloid kidney*, which is now rarely classed as a form of Bright's disease, or as an inflammation of the kidney, although it is recognized as occurring not infrequently in connection with, or as a complication of, a true nephritis.

There remain two groups of the chronic nephritides whose clinical features present such striking contrasts that, for purposes of description, one feels warranted in making separate classes of these groups. The justification of this seems apparent when one sees that corresponding to these two types, kidneys are found differing as markedly as do the clinical manifestations.

It is important, of course, that the names used to designate these two different kidneys should be as accurate as possible in describing the actual pathological condition present. But it is really of greater importance that the fact of the existence of these two types should be clearly recognized no matter what name be given. To the one form, characterized by œdema with abundant albuminuria and cylindruria the name *chronic parenchymatous nephritis* has been most often applied; to the other, with its marked cardiovascular changes, its relatively slight albuminuria and cylindruria with its abundant urine of low specific gravity, its frequent uræmia, the term *chronic interstitial nephritis* is given. As synonyms for the former may be mentioned large white kidney, large yellow kidney, chronic desquamative and chronic tubal nephritis, etc.; for the latter, contracted kidney, cirrhosis, sclerosis, granular atrophy, gouty kidney, etc. The former is the large, rather soft kidney, pale or darker—depending on the amount of fatty degeneration and of blood—with a capsule easily stripped, wide cortex, and with changes chiefly in the parenchyma, *i. e.*, the tubular and glomerular cells. The kidney of the second class is the small, rough, firm kidney, with adherent capsule, granular cut surface, thinned cortex, retention cysts, and with greater increase in the interstitial tissues.

While these are types and while they are seen with all their classical text-book features, both at the bedside and on the autopsy table, great variations from the type are frequently met with. Heubner rightly says that the majority of chronic kidney conditions are, according to generally accepted types, atypical. This has led to the naming of subclasses and varieties, tending in general toward complication rather than simplification. On close examination, it is seen that the names parenchymatous and interstitial are in reality misnomers, for with every parenchymatous nephritis the interstitial tissue is involved, and parenchymatous changes are seen in every case of chronic interstitial nephritis. The process is in reality a diffuse one—a *chronic diffuse nephritis*. In the one case the parenchyma is chiefly, and perhaps primarily, involved, and there is little or no induration or contraction; in the other, the interstitial structure shows the chief, perhaps the primary, change, and there is contraction or induration. Hence we have Senator's two classes of (1) chronic diffuse nephritis without induration; (2) chronic diffuse nephritis with induration. By diffuse is not meant that every part of the two kidneys—Bright's disease being a bilateral affection—is involved; as is well known, circumscribed foci of inflammation are often a striking figure in the kidney of nephritis, the "patchy" areas showing pathological change contrasting strongly with the healthier areas.

By diffuse is meant diffuse in the sense that the parenchyma and interstitium are both involved.

In practice the cases do not permit of such easy distribution into appropriate pigeon-holes as one might think. The pathologist often refuses to say more than that there is a chronic nephritis; and the clinical manifestations may be a mixture of the findings of the two classes. How often do we see cases with moderate œdema, urine quite rich in albumin and casts, about normal as to amount and specific gravity, the cardiovascular changes marked, perhaps also an albuminuric retinitis. Clinically it is a hybrid; postmortem it is in the mixed class. We must be content with the diagnosis of chronic nephritis or chronic diffuse nephritis. Repeatedly the writer has seen pathologists like Chiari, for example, one of the acutest diagnosticians of gross morbid anatomy, make the diagnosis of morbus Brightii chronicus, refusing to attempt to classify the specimen. This point, it seems to the writer, deserves especial emphasis, for much energy is wasted and much needless disappointment experienced in the attempt to make a given case fit into a classification that is largely artificial and necessarily imperfect. It is better for teacher, student, and practitioner to have a frank understanding on this point and to realize that disease often refuses to conform to the picture of the classical type.

This existence of the *mixed forms, i. e.*, the failure of the disease to conform strictly to a definite type, is recognized by many writers, although many still feel urged in every case of nephritis to attempt the impossible and to try to make a typical case out of an atypical one. Virchow,[1] in his *Cellular Pathology*, speaking of his three forms of Bright's disease, says: "The three varieties do not always occur as well-defined varieties, clearly distinct each from the other; it is more apt to be the case that two or even all three of these forms occur at the same time, and in the same kidney." Bartels says there are cases in which these forms are combined with one another in a variety of ways. Senator is explicit in his statement that one must often rest content with the diagnosis of chronic nephritis, not pretending to state the variety. Dieulafoy[2] makes three groups: (1) Chronic nephritis with a large kidney; (2) chronic nephritis with a small kidney; (3) an intermediate form, which is "the common form of Bright's disease." The same recognition of the mixed type is made by Welch in Flint's *Practice of Medicine*.

In some cases the view of Frerichs and of Reinhardt that the contracted kidney is a later form of the parenchymatous seems to be confirmed. At the bedside this transformation of a chronic parenchymatous nephritis into the chronic interstitial is occasionally seen, and postmortem a condition of secondary contraction is recognized. If we preserve the term chronic interstitial nephritis for the indurated or contracted kidney, it might be well to adopt the expressions *secondary interstitial nephritis* for this form and primary interstitial nephritis for the slowly developing, insidious, cardiovascular, typical contracted kidney.

As a subhead under chronic interstitial nephritis should be placed the *arteriosclerotic kidney* or granular kidney, with its striking local vascular changes that are but a part of a more general arteriosclerosis. This can generally be recognized at autopsy, and may be suspected and permits of a probable diagnosis during life, particularly in the aged.

[1] Quoted by Bartels, *loc. cit.*, p. 182.
[2] *Manuel de Pathologie Interne*, 12th ed., ii, p. 26 et seq.

The classification, then, that seems the best is practically that of Senator. It is one that appeals to the clinician as well as to the morbid anatomist. The term "parenchymatous" may be used in place of "diffuse without induration," because, although not literally expressive of the real condition, which is more or less diffuse, it recognizes what is true, that in this form the parenchymal changes predominate, they are quantitatively greater than in the second variety, in which the process, while diffuse, produces chiefly interstitial or stromal changes with resulting induration. The classification would be as follows:

1. Chronic parenchymatous nephritis. (Chronic diffuse nephritis without induration.)
2. Chronic interstitial nephritis. (Chronic diffuse nephritis with induration.)
   - (*a*) Primary chronic interstitial nephritis.
   - (*b*) Secondary chronic interstitial nephritis.
   - (*c*) Arteriosclerotic kidney.
3. Mixed type, a combination of 1 and 2, *i. e.*, diffuse nephritis.

ETIOLOGY OF NEPHRITIS.

In some instances the kidney is involved by a *direct extension* of inflammation from a neighboring structure. Such, for example, is the case in the ascending nephritis consecutive to pyelitis—pyelonephritis.

But the cause of the great majority of cases of nephritis is *hæmatogenic*. Some substance carried by the blood to the kidney acts as the excitant of inflammatory or degenerative changes, acute or chronic as the case may be, and the result is a nephritis, or an atrophic process that in its results is akin to a true nephritis. When we come to think of it, the wonder is that the kidney is not oftener involved than it is, for, acting as the important eliminating organ, it must be repeatedly subjected to insults in its efforts to eliminate the toxic substances present in the blood in the mild and severe infectious diseases to which man is liable, while excesses and errors in the matter of food and drink, and faults of metabolism must often charge the blood with material that might easily be harmful to the renal parenchyma.

These causes may for purposes of description be classified, although the distinctions are here somewhat artificially made; and in reality the operating etiological factor in a given case is often not a simple one, but a combination of two or more of the causes mentioned in these different groups. A working classification may be made as follows:

1. The infectious diseases, acute and chronic.
2. Chemical, *i. e.*, toxic substances, acute or chronic in their action. (*a*) Exogenous. (*b*) Endogenous. (i) Gastro-intestinal. (ii) Metabolic products.
3. Cold. *Nephritis a frigore.*
4. Pregnancy.
5. Heredity.

1. **The Infectious Diseases.**—Infectious diseases may as a class be regarded as the cause of a large percentage of cases of acute nephritis. Many cases that seem at first sight due to causes that are not microbic, often on close analysis are found to have been preceded by definite symptoms of an infection, mild perhaps or even unheeded by the patient himself, but yet

presumably the *fons et origo* of the later renal complication. A comparatively insignificant angina, a mild rheumatism, a "cold" or supposedly trifling "la grippe" may be the precursor of a nephritis. And in not a few instances an ambulatory and untreated scarlet fever or diphtheria has resulted in a nephritis. The severest case of acute nephritis with recovery seen by the writer was in a child whose scarlatina was overlooked by the parents until the arthritis ("scarlatinal rheumatism") caused them to consult a physician.

Among the infectious diseases attended or followed by acute nephritis *scarlet fever* stands preëminent. Even before the time of Bright, clinicians had noted the now well-recognized complication. What percentage of scarlatinal patients have nephritis it is hard to tell; the percentage differs in different epidemics. Not much reliance can be placed on statistical statements concerning the number of cases of acute nephritis that are due to scarlet fever. Much of the discrepancy between statistics of different observers may be explained by the fact that no hard and fast line is drawn between the albuminuria occurring about the third or fourth day—the so-called febrile albuminuria, and the later albuminuria, cylindruria, œdema, etc., or what is in the stricter sense the true scarlatinal nephritis. Traces of albumin with occasional casts can be found in more than half the cases of scarlet fever when the urine is repeatedly examined. If these are to be classed as instances of nephritis, the percentage is certainly high. The true nephritis is much rarer. Tirard quotes Turner as finding acute nephritis in 31.1 per cent. in 6000 cases of scarlatina, while Goodhall, in 5443 cases, found the incidence of nephritis to be 8.4 per cent. These latter figures, representing the real nephritis, are probably more nearly correct.

But without stating it in figures, it is sufficient to know that experience the world over, in hospitals and in private practice, and with various kinds of treatment, has demonstrated the great frequency with which scarlet fever is accompanied by acute inflammation of the kidneys. There would seem to be some selective action on the part of the infectious or toxic agent present in this disease for the kidney and even for one particular part of the kidney viz., the glomerulus. Often the other clinical manifestations of scarlatina are on the wane or have entirely disappeared; often the whole course of the illness has been mild, yet the nephritis occurs. During an epidemic of scarlet fever it is no uncommon thing to find nephritis in the patient whose other manifestations seemed the mildest. The writer saw an acute nephritis develop in a young man whose two sisters were ill with the most malignant type of scarlet fever, while the brother had but a mild angina with fever of 100° for two days, but no rash or other evidence of the disease. Why the kidneys should be so peculiarly vulnerable in this malady is not known. It was thought at one time to be due to the fact that there was such a marked involvement of a large surface of the skin, and the destruction or perversion of function of the skin was supposed to have a decidedly deleterious action on the kidneys, by causing them to perform the eliminating function of the skin as well as their own. But in smallpox, with more serious skin lesions, nephritis is less common than in scarlet fever. Scarlatinal nephritis is more likely to occur during the third or fourth weeks of the illness, *i. e.*, after the acute febrile period has been passed. The occurrence of nephritis late in the course of the primary disease is not peculiar to this acute infectious fever. Many other complications of acute infections are late in their appear-

ance, so there is nothing apart from the rule in the occurrence of nephritis at this time. One has only to think of empyema and arthritis in pneumonia, thrombophlebitis in typhoid, or arthritis in scarlet fever to see that it is the rule for many complications to appear late in the course of an acute infection.

The influence of exposure to cold during convalescence from scarlet fever has probably been exaggerated, as has the effect of error in diet, although they must be considered as contributory factors. Constipation or other alimentary disturbance may aggravate a tendency to acute nephritis under these circumstances, by permitting the absorption from the alimentary canal of deleterious toxic substances. Mahomed has found as premonitory evidence of acute nephritis, constipation, a high tension pulse, and red blood coloring matter in the urine, although no albumin could be found. Rosenstein[1] has noticed the pre-albuminous presence in the urine of red and white blood corpuscles and of cylindroids. Undoubtedly in some cases of scarlatinal nephritis there is a combination of operative causes. While the toxin present in the blood of scarlatina must be regarded as the primary cause, exposure to cold, errors in diet, constipation, or the use of alcohol may assist.

Diphtheria is by a few writers declared to be productive of more cases of acute nephritis than scarlet fever. By them the transitory acute parenchymatous degeneration with its trace of albumin in the urine is classed as nephritis. This so-called febrile albuminuria is so frequently found in diphtheria that its presence was long regarded as of great diagnostic importance. Since the diagnosis of diphtheria is now largely bacterial, less attention—perhaps too little—is paid to the albuminuria. Disregarding this febrile albuminuria, acute nephritis is by no means as common in diphtheria as in scarlatina. Acute nephritis in this disease is manifested in much the same manner as in scarlet fever, although it is more apt to make its appearance earlier. Since the use of antitoxin it is of rarer occurrence. It may be interesting to note that one of the earlier proofs that it was the toxin in many infectious diseases and not the organisms themselves that induced the nephritis was afforded by the injection of diphtheria toxin into animals, with the subsequent development of nephritis.[2]

Bright's disease as a complication of the other common infections of childhood is comparatively rare. Yet occasionally it is seen in *measles*, *German measles*, *chickenpox*, *whooping-cough*, and *mumps*. It may occur in *epidemic cerebrospinal meningitis*.

A trace of albumin with a few casts is a common finding in *typhoid fever*, disappearing with the subsidence of the fever. True nephritis is rare, and Bartels[3] saw but two instances in 1000 cases. The renal symptoms may appear early and for a time be the most striking feature of the case, constituting the so-called renal typhoid, or, later, during the height of the disease, or as convalescence sets in, the kidney may become involved. When we consider that in typhoid fever there is a true bacillæmia, and that in about one-quarter of the cases typhoid germs during convalescence are present in the urine, and that in such kidneys little clumps of bacilli are to be found, from the breaking down of which "nests" into the tubules the bacilli gain

[1] *Pathologie und Therapie der Nierenkrankheiten*, fourth edition, p. 158.
[2] Roux and Yersin, *Annales de l'Institut Pasteur*, 1888.
[3] *Ziemssen's Encyclopædia.*, xv, 527.

entrance into the urine, the wonder is that typhoid nephritis is not of more frequent occurrence. It is such cases as these that make the term "toxic infectious," employed by Dieulafoy[1] to designate this whole group of nephritides accompanying the infectious diseases, peculiarly applicable.

In *pneumonia* casts and albumin can usually be found. In a series of consecutive cases the writer found in each instance at some time during the illness a trace or more of albumin and a few hyaline or granular casts. True nephritis is comparatively rare. It may appear during the height of the disease or during convalescence. In some of the cases of acute nephritis found in pneumonia, as in other infections, the renal trouble is merely an aggravation of a previously existing chronic nephritis, *i. e.*, an acute exacerbation. Early in all infections a careful examination of the urine, the cardiovascular system, etc., should be made, so that the nature of any complication that may arise in the kidney may be more definitely recognized. In pneumonia, as in typhoid, the specific germ has been found in the kidney, so that the question as to what extent the nephritis is due to the microbe *per se* and to what extent to the toxin is a hard one to decide.

With *typhus fever* and *smallpox* acute inflammation of the kidney is common. It has been seen in *vaccinia*. In *cholera* the scanty, bloody, and albuminous urine is found associated with an acute destructive degenerative change in the kidney. In *yellow fever* and *acute yellow atrophy of the liver*, acute degenerative and inflammatory lesions are frequently found in the kidneys, and the symptoms of acute nephritis are present during life. In *relapsing fever* acute nephritis has been noted (Ponfick).

Malaria often induces nephritis apart from the hæmoglobinuria or blackwater fever. Kelsch and Kiener insist upon the occurrence of malarial nephritis. Thayer analyzed the Baltimore cases and found acute nephritis in over 4 per cent. of the patients with æstivo-autumnal infection. The so-called febrile albuminuria is found in a much larger percentage—probably one-half—of cases of acute malaria.

Considering the great frequency of *rheumatic fever* and *chorea*, nephritis must be regarded as a rare complication of these diseases, yet it is occasionally seen. If, however, we regard some of the anginas of obscure origin and some of the *purpuras* as rheumatic in character, rheumatism must be looked upon as a not infrequent cause of nephritis. It is not unusual to see a patient whose illness began with sore throat, joint pains, and purpuric manifestations, in whom œdema, albuminuria, hæmaturia, cylindruria, etc., give unmistakable evidence of an acute nephritis. In *erythema nodosum*, also, nephritis is reported.

As has been already said, a *tonsillitis*[2] or an every-day sore throat is probably in many instances the atrium for the entrance of toxic infectious agents that induce nephritis, and in all cases of obscure origin careful inquiry should be instituted as to recent throat or nose trouble.

With *erysipelas*, febrile albuminuria is common; true nephritis occurs, although not often. Nephritis has also been reported in *dysentery*.

With *septicæmia* and *pyæmia*—due to a streptococcus, staphylococcus, pneumococcus, gonococcus, etc.—febrile albuminuria is the rule. True nephritis also is not uncommon. In some instances the nephritis is clearly

[1] *Pathologie Interne*, 1900, tome ii, 17, 18.
[2] Cf. Morse, *Archives of Pediatrics*, 1904, xxi, 337.

metastatic, mycotic emboli from a thrombosed vein or from infected cardiac valves lighting up the nephritis or perhaps producing a suppurative nephritis or surgical kidney. But aside from the embolic variety, acute nephritis—"toxic infectious"—in the course of sepsis is frequently seen. Possibly some of the instances in which nephritis is recorded as due to a *skin disease* are in reality of the nature of "toxic infectious" inflammations, the skin lesion being suppurative or furnishing a portal of entrance for germs. In a similar way *alimentary disturbances* may be microbic and the nephritis that perchance results might be classed under the head of infectious, although toxins are probably the direct exciting cause.

Acute or subacute parenchymatous nephritis is often seen in *tuberculosis*. Some of the supposed cases of nephritis with tuberculosis are amyloid. Perhaps, too, secondary infection with pyogenic microbes explains some of the cases of Bright's disease complicating tuberculosis. While tubercle bacilli may lodge in the kidney itself, that organ is permeable for this germ. French writers particularly call attention to experimental glomerular and tubular nephritis in lower animals produced by injecting tuberculin. But whether one looks upon the tuberculous toxin as the cause of the complication, a view that has some experimental and clinical support, or regards the tuberculosis as merely a predisposing cause, and exposure to cold, use of drugs, overfeeding, use of alcohol or a secondary infection as the real cause, certain it is that nephritis is quite common in tuberculosis.

Influenza is also a cause of nephritis. During the epidemic in the preceding decade the unusually large number of cases of acute nephritis excited general comment among practitioners.

Occasionally cases have been seen in which the question of the existence of some *specific germ* for acute nephritis has been raised. Saundby cites Fiesinger,[1] who described what appeared like an epidemic of nephritis, no other localization of the infection than in the kidney being manifest. Black Milne[2] saw three children in one family and two in another, sick at the same time with acute nephritis. No common cause, such as exposure to cold, was found, and Dr. Milne raises the question as to the possible common microbic origin with a special tendency to localization in the kidney.

The controversy concerning *syphilis* as a cause of nephritis has not yet quieted down. There are those who regard the inflammation of the kidneys in a syphilitic as due to the drugs employed, especially the mercury, to the influence of cold (Bradford), to accidental causes, such as alcoholism, to other infections, etc. Klieneberger,[3] in Lichtheim's clinic, made a careful urinary study of 31 patients, some of whom were non-syphilitic, who were treated by mercurial inunctions. With great uniformity he found evidence of irritation of the kidney in the presence of albumin and casts, and while advocating the use of mercury in the treatment of syphilis, he feels that the remedy should be used cautiously and the effects on the kidney carefully noted, for, as he says, this is not an "indifferent" treatment. Wagner suggested that the angina often seen in syphilis might be the intermediate agent in producing nephritis by affording an avenue of admission for harmful germs. It is difficult to settle the question on the basis of clinical evidence alone; the fact that nephritis appears during the course of an

[1] *Rev. de Méd.*, 1893, p. 404.
[2] *British Medical Journal*, 1892, ii, 1391.
[3] *Zeitschr. f. klin. Med.*, 1906, lviii.

active syphilis does not prove conclusively that it is due to the syphilis. Yet so many observers have seen an inflammation of the kidney appear in a syphilitic, especially in the secondary stage of the disease, before mercury had been given, when exposure to cold, as well as the influence of alcohol could be eliminated, and when there was no reason to suspect the existence of any other infection, that the conclusion has been forced upon them that the nephritis was syphilitic in origin. The good influence of antisyphilitic treatment in some cases is also an argument advanced to show this causal relation. Such a case, to cite an example, is that reported by Mühlig[1] of acute parenchymatous nephritis, due, as he believes, to syphilis and which appeared fourteen days after the initial lesion and several days before any of the ordinary secondary manifestations of syphilis. Recovery was prompt under intramuscular injections of bichloride of mercury; no good results had previously followed from treatment by sweats and milk diet. Max Wagner[2] concludes that mercury is not contraindicated in parenchymatous luetic nephritis; it should merely be given cautiously. The good curative effects commonly seen from mercurial treatment seem to point to the fact that the nephritis is in reality of syphilitic origin. The writer's experience tallies with that of those who regard syphilis as a potent cause of acute nephritis, especially in the first two years after the initial lesion.[3] One is inclined to believe with Dieulafoy: "La syphilis est une cause puissante de néphrite aiguë," although not, perhaps, venturing to go as far as does Chauffard,[4] who, basing his diagnosis—as Mauriac asserts one must in such cases—more upon instinct than upon material proof, declares that acute nephritis during secondary syphilis is due solely to syphilis and its virus, as is shown by all contemporary observations.

Of the influence of syphilis in producing chronic sclerotic changes in general, including such changes in the kidney, there is little question.

Practically every known infectious disease has been recorded as having been at times accompanied or followed by an acute nephritis. The fact, however, that an acute inflammation of the kidney accompanies, or follows hard upon, an infectious disease does not of necessity prove that the particular microörganism producing the infectious disease, or its toxin, is also causing the nephritis. While this is presumably so, it may often be that the infectious disease merely paves the way for some secondary and intercurrent microbic or toxic agent that acts upon the kidney under these, for the kidney, unfavorable conditions. Nothing definite is known that will explain why in one case of acute infectious disease the kidneys escape, while in another they are hard hit. Variations in the amount of toxin, its virulence, or the length of time it acts must be assumed to aid in the explanation. Differences in the make-up of the kidney and its resisting power or sensitiveness to harmful influences, and differences in the resisting power of the body as a whole, must be inferred. As has already been said, it is probable that occasionally the kidney is already the seat of an overlooked chronic nephritis or passive congestion, and the acute nephritis is in reality of the nature of an exacerbation of an already existing trouble. A once damaged kidney may be

[1] *Münch. med. Woch.*, 1903, No. 12.
[2] *Ibid.*, 1902, Nos. 51 and 52 (contains numerous references).
[3] The subject of syphilitic nephritis has been recently treated by Josserand, *Lyon Médical*, November, 1904.
[4] Chauffard et Gouraud, *La Presse Médicale*, 1902, liv, 639.

peculiarly liable to become again seriously affected. Recovery may have ensued in a clinical or functional sense, yet a recovery with some permanent weakness or defect. But the entrance again into the body of microbes or the springing into activity of microörganisms that have long lain dormant and apparently harmless in the body—typhoid bacilli in the gall-bladder, gonococci in the prostate or Fallopian tubes, streptococci or staphylococci in the middle ear or in an ancient osteomyelitis—may lead to a fresh acute outbreak in the kidney that had apparently recovered, but now shows itself peculiarly sensitive to even slight insults.

A selective affinity of the toxins of certain diseases, *e. g.*, scarlet fever, for the kidney may also be assumed to explain the unusual frequency of Bright's disease with some infections, its rarity with others. Very suggestive work has been done by Forssner,[1] who found that a streptococcus that showed no special predilection for lodgement in the kidney, by being grown in extract of kidney or in kidney itself, acquired some property by which when now injected intravenously it produced local renal lesions. An affinity for certain tissues, *e. g.*, the kidney, might therefore be acquired as in cases of scarlatina by an organism like the streptococcus, that would help to explain how, in certain instances instead of producing general septic processes it would lead to some local inflammation, as in the kidney. While the microörganisms present in the kidney itself may be the cause of nephritis, it is far more common, according to the general belief, supported by experimental, clinical, and anatomical investigation, to have the nephritis excited by the chemical irritant—the toxin—that is produced in the body when invasion by microbes has occurred.[2]

And these organisms, or rather their toxins, often display a selective affinity for certain parts of the kidney, one organism damaging particularly the glomeruli, another the tubular epithelium, or another the interstitial tissue. The lesions, too, are with some organisms chiefly exudative and proliferative *i. e.*, truly inflammatory, with others degenerative or again often characterized by hemorrhages or interstitial cellular accumulations. These anatomical changes, which seem almost pathognomonic, are often accompanied by clinical manifestations that are likewise peculiar, so that by qualitative and quantitative urinary changes the presence or absence of œdema, cardiovascular lesions, etc., it is possible at times to recognize the nephritis as clinically like that due to some particular organism, although the details of these special forms of nephritis are as yet far from distinct and clean-cut, nor can it yet be said that any one etiological factor always produces one and the same anatomical or clinical picture.

It is along these lines that much clinical and pathological observation as well as experimental work is needed, for it is only in this way that the much to be desired classification of nephritis on an etiological basis can be secured, carrying with it the possibility of better results in the way of prophylactic or perhaps curative therapy. And it is in this way, too, that many of the facts, still obscure, concerning the physiology and pathology of the kidney may be learned, such as the relation between the renal lesion and albuminuria, polyuria, hæmaturia, etc., the origin of casts, the significance

[1] *Nord. med. Archiv*, 1902, Abt. ii. Heft 4. No. 18.

[2] Cf. Paul Asch, *Ueber den Einfluss der bakteriellen Stoffwechselprodukte auf die Niere*, Strassburg, 1904.

and real cause of high blood pressure and of uræmia, and why these are marked in one form of nephritis and not in another. But as clinicians we should not forget in our eagerness to predict with as much accuracy as possible the exact anatomical lesion to be found in a given case, that this lesion is, after all, but a part of the disease manifestation in the same way that hard pulse, headache, or albumin may be, and we should aim to go back of this and strive for ability to detect etiological factors that may be remediable. In the light of our present knowledge it is often better, as Müller says, to make a clinical diagnosis and a classification based on anamnesis and clinical symptoms than an unsatisfactory attempt to predict anatomical postmortem findings. Müller would be better satisfied with a clinical diagnosis of "chronic disease of the kidney with dropsy" (chronische hydropische Nierenerkrankung) than with "large white kidney" or "chronic parenchymatous nephritis," for the former is clinically accurate, the attempted anatomical diagnosis may be, probably is, but partially correct.

2. **Toxic Agents.**—While the true nature of the poisons that produce nephritis in the case of the infectious diseases is not known, and while many of the more strictly toxic nephritides are due to poisons whose origin in the body is obscure and whose chemical composition is still unrecognized, there are certain known toxic substances that are capable, when introduced into the body in large enough amounts, of producing an acute nephritis; and others capable of inducing a chronic change in the kidney, provided the action be extended over a long period of time.

(*a*) **Exogenous Toxic Substances.**—Of the exogenous toxic substances, a long list might be given, including certain organic and inorganic chemicals used as *drugs*, and others whose entrance into the body is always a matter of accident or due to an intent to harm. Such substances are cantharides, turpentine, carbolic acid, chlorate of potassium, salicylic acid and its compounds, oxalic acid, the mineral acids, bichromate of potassium, alcohol, chloroform, phosphorus, mercury, lead. Long-continued action of many of these substances in smaller amounts, *e.g.*, lead or mercury, may induce chronic nephritis. Morphinism may be a cause. Even chloride of sodium, which has at times been employed for the production of inflammatory and degenerative lesions of experimental nephritis (Stokvis, Levi, Castaigne and Rathery), and the harmful influence of which in the aggravation of the œdema and albuminuria of nephritis is well known, has been regarded as an occasional cause of acute nephritis[1] when used in large doses. The innocuousness as regards the kidneys of the curative *sera*, of tuberculin, of vaccine virus, etc., is one of the fortunate facts concerning these valuable diagnostic and therapeutic agents, but whether in exceptional instances a toxic nephritis may not be lighted up is not definitely settled. The effect on the kidney of the injection of the vaccines in the treatment along the lines of the so-called "opsonic therapy" of Wright must also be carefully watched. In *ptomaine* poisoning damage may be done to the kidneys by ingested poisons. The whole question of the effects of adulterated *food* on the kidneys is one requiring careful consideration, and the use of such adulterants calls for proper legal restrictions. The question may also be raised whether at times a nephritis may not be induced by the excessive quantity of food, *e. g.*, meat, that is eaten, overwhelming the kidneys by the quantity rather than the quality

[1] Cf. Tarino, *La Presse Médicale*, 1904, xxviii, 222.

of the digestive and metabolic products. The too free use of highly seasoned foods has also been held responsible for some cases of nephritis.

The exogenous toxic substances do not of necessity always enter by way of the alimentary tract. Chloroform may be a possible excitant of nephritis, even when inhaled. The external application of drugs has in numerous instances been held reponsible for inflammation of the kidney. Care should always be exercised in the use on the skin, and particularly when the surface of the skin is broken, of such remedies as carbolic acid, turpentine, bichloride of mercury, iodoform, pyrogallic acid, naphthol, and the preparations of tar. Recently a case of acute nephritis has been reported in which the cause seemed to be the extensive application of balsam of Peru.[1] A case of acute nephritis in a man aged twenty-six years is reported by Gassmann,[2] in which severe urinary symptoms and œdema appeared after the external use for two days of 25 gm. of balsam of Peru with sulphur, for scabies, one-third of the body being anointed with the salve. Gassmann gives references to some six or seven other similar cases in which balsam of Peru externally applied produced acute nephritis.

In some lesions of the skin, such as eczema, the nephritis that is occasionally seen as an accompaniment is perhaps due to the formation of some toxic product in the diseased skin. Extensive *burns*,[3] as is well known, are peculiarly prone to be followed by acute, often severe changes in the kidney, due to toxic substances resulting from the destruction wrought in the skin. Some, however, regard the hæmolytic changes wrought in the blood through the agency of the burn as the cause of the toxic symptoms seen clinically, and of the anatomical alterations that take place. The intestine and kidney are the chief avenues of elimination of this poison, and often show the most marked pathological lesions. The poison is in some respects comparable to the snake venoms.

The long-continued use of the *Röntgen rays* may not be without harm to the kidney. This probably arises more from the destruction of leukocytes, and of lymphoid or neoplastic tissue, with the development of toxic substances that are injurious to the kidney, than from the direct harmful effect of the ray upon the kidney itself. Warthin[4] describes inflammatory and fibrotic changes with remarkable lime-salt deposits in the kidneys of patients with myeloid leukæmia and Hodgkin's disease who had been treated for a long time with the Röntgen rays. Toxic symptoms referable to the nervous system have, as is well known, been not infrequently observed in patients with leukæmia undergoing *x*-ray treatment. The necessity of careful watching of the urine in such patients is clear.

(*b*) **Endogenous Toxins.**—Most of the endogenous toxins are as yet unidentified, but it is possible that not a few of the cases of acute nephritis may be due to toxic substances rapidly formed within the body.

(i) Acute gastro-intestinal disorders at times seem to be the starting point of acute nephritis. Here, in many instances at least, microörganisms or irritant chemicals have been introduced from without, but the disturbed conditions in the alimentary tract give rise to the formation of new toxic products which when absorbed act harmfully upon the kidney. Acute nephritis

[1] L. H. Hoffman, *Journal of the American Medical Association*, 1907, p. 2086.
[2] *Münch. med. Woch.*, 1904, No. 30.
[3] Literature on burns in Pfeiffer, *Virchow's Archiv*, 1905, clxxx, 367.
[4] *American Journal of the Medical Sciences*, 1907, cxxxiii.

of this type, *e. g.*, occurring in connection with the acute gastro-enteritis of children, is a good illustration of the frequent combination of causes of various kinds, microbic and chemical, exogenous and endogenous. It does not seem a rash assumption regarding many cases of chronic nephritis of otherwise obscure origin to look upon *digestive disturbances* as the etiological factor. Errors in diet, and digestive functions faultily performed may easily be regarded, if continuing for a long period, as leading to chronic toxæmias, with resulting renal changes. In some instances bacterial growth in the bowel may be excessive and toxins increased in quantity, or the change may be qualitative rather than quantitative, the bacteria being different in kind. Or we may conceive of some protective chemical process in the bowel or liver, as being deficient under pathological conditions, and a toxin that in health is rendered harmless, being left free to be absorbed and in this way reach the kidney and induce inflammation.

In children malnutrition with its gastro-intestinal disturbances may cause nephritis. This is seen in infants in hospitals and asylums.[1]

When we broaden the conception so as to take in *disorders of metabolism* we may find a probable explanation for many chronic nephritides. But little definite knowledge is as yet possessed upon this subject, still one may imagine that faults on the part of such organs as the liver, pancreas, adrenals, thyroid gland, or even the muscles, might by malperformance of function, perhaps internal secretory function, lead to chronic renal disease. And the influence of excessive worry, anxiety, business hurry, and *nervous strain* in the production of chronic nephritis, a fact regarded by many as explaining the apparent frequency with which Bright's disease is seen in modern life, may be due to faulty performance of function on the part of some of the viscera through perversion of nervous influence, or even to the presence in undue amount of some obscure toxic material, the result of excessive overuse of nerve cells.

With *jaundice*, albumin and casts are often found in the urine. This result of the presence of biliary matter and perhaps other toxic material in the blood usually disappears with the disappearance of the jaundice, although rarely a genuine degenerative or inflammatory lesion of the kidney persists.

(ii) *Gout* stands as the type of metabolic disease in which chronic nephritis may develop. Long continuance of gout usually leads to more or less marked cardiovascular and renal sclerosis, presumably from the influence upon the heart, vessels, and kidneys of the chemical substances present as the result of faulty metabolism. In *diabetes*, also, chronic nephritis is occasionally seen. Here the nephritis is apparently toxic, although the influence of excessive quantities of food, with unusual demands on the kidney in the way of elimination, may play a part. The excessive work required of the kidney in diabetes may perhaps of itself result in nephritis, for in cases in which the entire renal function has been forced upon one kidney after its fellow has been removed, a nephritis has occasionally developed in the remaining, previously healthy, but now compensatorily hypertrophied, organ, thus seeming to show that excessive work *per se* may at times lead to nephritis. Obesity at times leads to sclerosis of the vessels, and contracted kidney may be found in the fleshy, especially, it would seem, in fleshy women.

It is in place here to refer to the observations of some who have found that

[1] Cf. Fry and Martin, *Archives of Pediatrics* 1904, xxi, 19.

when injured renal tissue has been left in the body, as where the kidney is left *in situ* after ligation of the ureter or the renal vessels, the cells of the remaining kidney may undergo degenerative changes, believed to be due to the nephrotoxins (isonephrotoxins) developed from the absorption of the damaged renal tissue. This has been thought to explain in part the progressive character of some cases of nephritis. Others, *e. g.*, Pearce,[1] while able to induce nephritis by using heteronephrolysins, have been unable to get positive results with isonephrotoxins.

3. **Cold.**—Cold is, perhaps, as Bartels[2] called it, an etiological scapegoat as regards nephritis. Yet we unquestionably see the influence of cold in the causation of such conditions as coryza, tonsillitis, and pneumonia, and clinical evidence is strong that at times exposure to cold precipitates an attack of acute nephritis or aggravates an already existing chronic nephritis. Just as in tonsillitis or pneumonia cold may favor the activity of pathogenic bacteria, so in the case of the kidney we may look upon cold as favoring the action of infectious or toxic agents that thus produce nephritis. How the cold works in these cases is not always clear. Elimination through the skin may be interfered with, throwing a heavier burden of work on the kidney, the driving of blood from the cutaneous vessels to those of the viscera may congest the kidney, or there may be some injurious change wrought in the blood, with resulting toxins. Any one or all of these causes may, perhaps, help in the lighting up of a nephritis and serve as a partial explanation at least, for the appearance of nephritis after exposure to cold. Changeable climate seems to favor the development of nephritis. Eichhorst saw relatively more cases on the East Prussian Coast than in the more equable climate of Jena and Berlin. Similar observations are recorded by Saundby and by Frerichs.

4. **Pregnancy.**—Pregnancy has been recognized as a cause of nephritis since Rayer first called attention to the fact. There are certainly two conditions that have to be here considered. In the first place, some of the cases of nephritis complicating pregnancy are cases in which a previously existing, but unrecognized, nephritis has been aroused to fresh activity through pregnancy, which may be looked upon, therefore, as merely aggravating the condition. But in the second group are the cases in which kidneys previously healthy are injured during pregnancy, as shown by anatomical study as well as by urinary findings and the clinical symptoms of eclampsia. The cause of this disease of the kidney is still not clear. Rayer and others emphasized the importance of increased intra-abdominal pressure due to the pregnant uterus, and particularly direct pressure upon the vessels of the kidney or upon the ureter. Such pressure might result in circulatory and degenerative changes in the renal parenchyma. There seems to be a greater frequency of the kidney of pregnancy in primiparæ, whose walls are more unyielding and therefore favor firm pressure, and in whom the uterus is more apt to be large from twin pregnancy and hydramnios.

Toxæmia, however, undoubtedly plays an important part, as Virchow insisted. Pregnant women are often, through false notions of modesty, through fear, or because of indisposition, confined to the house, taking insufficient exercise and neglecting even the customary care of the skin. They are often obstinately constipated. Elimination is, therefore, deficient and

[1] *University of Pennsylvania Medical Bulletin*, 1903, xvi, 217.
[2] *Ziemssen's Encyclopædia*. American edition, xv, 254.

toxæmia favored. Metabolic processes, while active, may be perverted, and toxæmia result. Besides, extra demands are made upon the mother, not only in the way of supplying nourishment for the developing fetus, but also in the way of elimination, and often under very unfavorable physical conditions. These questions will be again taken up in the discussion of puerperal eclampsia and the kidney of pregnancy.

5. **Predisposing and Contributing Causes.**—**Heredity.**—There can be no question that a tendency to nephritis is at times transmitted. Nearly all writers refer to this, and nearly every practitioner of wide experience has seen instances in which there is a remarkable family tendency to Bright's disease. This is often an hereditary arteriosclerotic tendency, the kidney sharing in the general vascular change. The chronic forms may even appear in childhood. In one family observed by the writer there is a history of renal trouble in the parents and several of the uncles and aunts; one woman of fifty has chronic interstitial nephritis, and her three daughters and one son have had albuminuria from the age of twenty at least, and cardiovascular changes are already in evidence.

Age.—The young are more liable to have the parenchymatous forms, because of their greater liability to infectious diseases. The so-called interstitial forms are oftener seen later in life.

Sex.—From greater exposure, severer physical work, and greater carelessness in the matter of food and drink, the male sex will show a larger percentage of cases of Bright's disease, although the influence of pregnancy and pelvic infections goes a long way toward increasing the percentage of cases in women.

Occupation may predispose to nephritis. Workers in lead or mercury, those helping about breweries or saloons, where alcohol is often taken freely, are especially prone to disease of the kidney. Engineers, workers in the cooling-rooms of packing-houses, and others engaged in occupations that expose them to extremes of heat and cold are peculiarly liable to the development of parenchymatous nephritis.

Other Diseases.—Diseases producing congestion of the kidney, *e. g.*, non-compensated disease of the heart, favor the development of nephritis. Acute nephritis may lead to the chronic form. And, as has been already mentioned, the infections often lead directly to Bright's disease, but probably at times indirectly, the debilitated condition of the patient favoring the action of any accidentally operating cause that might produce nephritis, but which, acting in an individual who was healthy, would be without harmful result. It is possible that prolonged mental strain and excessive wear and tear on the nervous system may have much to do in the way of predisposing to disease of the kidney.

CHAPTER VI.

ACUTE NEPHRITIS.

By JAMES B. HERRICK, M.D.

Etiology.—The ordinary causes—acute infections, intoxications, cold, pregnancy, etc., have just been considered and need not be repeated.

Pathology.—In acute nephritis both kidneys are involved, and usually equally involved. The kidney may be of normal size and show few or even no changes that can be detected by the naked eye. Ordinarily, however, it is somewhat larger than normal, and in exceptional cases the weight may be twice that of an average kidney. The tense kidney may bulge through an incision in the capsule like a hernia (Dieulafoy). The capsule strips readily. The color varies, depending largely on the amount of blood in the vessels, the hemorrhages and the fatty changes that have taken place; it is usually grayish red or quite dark red, the stellate veins often showing plainly. A more marked grayish, whitish, or yellowish tint is seen in cases of longer standing, say of four to six weeks' duration, where fatty and other degenerative changes are especially marked. The kidney usually feels rather soft. On section, the cortex is seen to be swollen, its grayish-yellow or lighter red color showing in sharp contrast to the deeply brownish-red pyramids. The cortex may show yellowish areas or streaks marking the degenerated tubular epithelium, with reddish lines representing the engorged vessels, or reddish dots due to the prominent glomeruli or to smaller or larger hemorrhages.

The microscopic study as well as clinical and experimental observation go to show that the changes are partly degenerative and partly inflammatory. Attempts to distinguish definitely between the purely degenerative and the more strictly inflammatory changes in these kidneys are by no means successful. In exceptional instances kidneys of the purely degenerative type are seen, or of the inflammatory, and it is best, perhaps, to describe the changes commonly seen without attempting to draw a sharp line between the acute degenerative and acute inflammatory lesions. Nor can a clear etiological differentiation be made, for toxins sometimes produce inflammatory lesions, while bacteria themselves may induce degeneration and necrosis.

There are certain anatomical peculiarities of the kidney of nephritis, characteristic of different operating causes. For instance, the lesions of scarlatinal nephritis are largely glomerular; in diphtheria the tubular epithelium first shows degenerative changes, especially in Henle's loop; in cholera the epithelium of the convoluted tubes is particularly involved. Similarly, in experimental nephritis[1] a selective action of the toxin employed is often seen. Thus, of chemical substances, chromium salts induce a tubular

[1] H. A. Christian reviews the recent literature on experimental nephritis in the *Boston Medical and Surgical Journal*, 1908, clviii, 416, 462.

nephritis, cantharidin affects chiefly the glomeruli, while vinylamin leads to necrosis of the medullary portions with inflammation of the renal pelvis, sparing the cortex. With uranium nitrate, as shown by Richter,[1] human nephritis is imitated as to dropsy. The description of the anatomy of the kidney of acute nephritis here given will be that of what may be called the typical acute nephritis, or, if one please, the "average" kidney of acute nephritis, as seen in clinical cases that come to autopsy.

The Malpighian Bodies.—One thing that strikes the observer who is studying the changes in the Malpighian bodies is the fact that very often some seem absolutely normal, while others, even those in their immediate vicinity, may show extensive lesions. This irregular distribution of the pathological process in the kidney is not, however, confined to the glomeruli, nor to acute nephritis. It is found, as will be seen later, in the other renal structures, and in other forms of Bright's disease, and is the more remarkable when we think that the operating cause is so often a toxin or soluble chemical substance in the blood that must come in contact with all parts of the kidney. In acute nephritis *Bowman's capsular space* contains red and white corpuscles, desquamated epithelial cells in various stages of disintegration, even to the extent of being represented by an amorphous, granular debris, and a fluid variously described as serous, albuminous, an inflammatory product, etc., often coagulated, and at times demonstrably containing fibrin threads. The amount of these substances may be very slight or so great as to compress the capillary tuft into a small space. And the proportion of the different ingredients may vary, in the one case the space being filled with an albuminous fluid or with granular material, in another with red blood corpuscles, this latter condition constituting one of the striking findings in some cases of hemorrhagic nephritis. In fact, in most instances, renal hæmaturia is of glomerular origin. The *cells of the capsule* may be normal, although many of them commonly show degeneration, as evidenced by their swollen condition, their granular or hyaline appearance, the presence of fat droplets, and the indistinct or vanished nucleus. Many of the cells are represented by ragged, irregular fragments only, and, as has been said, large numbers of cells may have dropped off and be seen in the capsular space. This leaves bare areas in the capsular wall, although the denuded spots may be rapidly covered by large numbers of newly proliferated cells, efforts at regeneration often being shown by mitotic figures. The crescentic masses, so commonly described in the Malpighian bodies of acute Bright's disease, are made up, according to some, of masses of these proliferated cells lying between the basement membrane of the capsule and the capillary tuft, while others (Ribbert) regard the masses as made up of desquamated glomerular epithelium.

The capillaries of the *glomerulus* are often tensely filled with blood that may be in thrombus form. Cells of uncertain nature, perhaps leukocytes, are sometimes seen in great numbers within the lumen. A hyaline appearance of the entire tuft is often noted. The cells covering the glomerular vessels have undergone the same changes just referred to in connection with the capsule. At times proliferation has been active, and little more can be made out than a compact mass of epithelial cells, with deeply stained nuclei. The tuft may be pressed to one side of the capsule, the mass of

[1] *Beiträge zur klin. Med., Senator Festschrift,* 1904.

exudate, blood, and broken-down cells in the capsular space, which exerts the pressure, being in the shape of a crescent or half-moon. The hyaline appearance just referred to is seen in the kidneys in many acute infections, and involves the capillary wall. It is particularly noticed in plague (Albrecht and Gohn, Duerck, Hamdi). Herzog,[1] however, finds the hyaline appearance in plague due rather to fibrin thrombi within the glomerular capillaries, and seen as well in the afferent and efferent vessels, and even in the other vessels, especially those of the cortex. Herzog's illustrations and descriptions seem very convincing as to the intravascular location of these hyaline thrombi. He believes them due to toxins rather than to the bacilli themselves.

It can readily be understood from a consideration of the glomerular changes just described that the plugging of the capillaries with thrombi, the filling of the capsular space with exudate and debris, with resulting pressure upon the vessels of the tuft and upon the tubules, must result in marked disturbance of glomerular function. In the glomerular lesion is found the main, although not the sole, explanation of the albuminuria, a partial explanation of the oliguria, and perhaps, through the obstruction that is offered to circulation, one of the causes of increase in blood pressure. Moreover, the circulatory disturbance in the capillaries of the glomerulus must contribute to the nutritional and functional disturbance of the tubular epithelium.

The glomerular lesions are the only ones seen to any extent in some forms of acute nephritis, hence the use of the term glomerulonephritis. Scarlatinal nephritis is often of this type. This peculiar involvement of the glomeruli alone suggests some selective affinity on the part of certain toxic substances for particular structures of the kidney.

The Tubules.—The same irregularly distributed or patchy arrangement of the diseased areas that was noted in the case of the Malpighian bodies is seen in a study of the tubules. Side by side may be seen tubules of normal appearance and those extensively diseased. The cells are swollen, hazy or granular in appearance, the nuclei indistinct or invisible. In other cells the nuclei may still remain, but the brush-like appearance of the cell has disappeared, and it looks hazy or hyaline. Fat droplets are frequently seen. The lumen of the tubule may be perceptibly narrowed by the swelling of its cells, although, at times, the lumen is increased because the cells are flattened or more or less disintegrated and their places taken by fragmentary relics, or they have entirely disappeared or are seen not in their proper places but in the tubules, showing all stages of disintegration, even to being represented by amorphous granular debris or drops of fat. Regenerative appearances are occasionally described. Red and white blood corpuscles are also seen in greater or less abundance, and casts of different kinds.

The increase in size of the lumen of the tubules may also be due to its blocking up by these substances and the damming back of the urine above this obstruction. These changes are oftener seen in the convoluted tubes or in the straight tubes, but may also be marked in the collecting tubes, *e. g.*, in vinylamin nephritis (Ehrlich, Heineke), although usually to a slighter degree.

[1] *Fibrin Thrombosis in the Glomerular and other Renal Vessels in Bubonic Plague*, Manila, 1905.

In some instances the lesions in the kidney are confined to the tubules, constituting the so-called tubular nephritis.

The Interstitial Tissue.—This may fail to show changes. Yet usually, even in some of the more recent cases, an inflammatory œdema is shown by the widening of the intertubular spaces. Round-cell infiltration may occur, especially in the neighborhood of the glomeruli. Hemorrhagic areas are not unusual. The vessels show varying degrees of engorgement. In cases of longer standing, such as perhaps might be termed subacute, proliferative changes in the connective tissue may be detected. This is sometimes well seen in a slight thickening of Bowman's capsule. A study of the kidney of acute nephritis soon convinces one that the term parenchymatous commonly applied is in reality a misnomer, for in nearly every case definite interstitial lesions can be made out, although the main alterations are found in the Malpighian bodies and in the tubules, *i. e.*, in the parenchyma. The justification for the term diffuse nephritis, insisted upon by many, is thus clearly seen.

In some instances, especially of acute infections, the striking or even the sole change is seen in the interstitial tissue, which may be the seat of an inflammatory œdema, but whose chief feature is the presence, sometimes focally, at others more diffusely, of larger or smaller numbers of cells that have been variously described by different writers, but which have been shown by Councilman[1] to consist in large measure of cells identical with Unna's plasma cells. These are large roundish or oval cells, with a well-staining protoplasm, a non-vesicular nucleus or nuclei, generally eccentrically placed, the nucleus containing deeply staining granules, and with mitotic figures quite common. The cell may originate from lymphocytes, perhaps at a distance, *e. g.*, in the spleen or marrow, is carried to the kidney, whose vessels it leaves by virtue of its amœboid properties, either as a plasma cell or its forerunner the lymphocyte, and helps to make one of the striking features of the round-cell infiltration in the "acute interstitial nephritis."

The foci in which these collections of lymphoid and plasma cells are found are especially in the boundary zone of the pyramids, in the subcapsular region of the cortex, and around the glomeruli. The condition was found by Councilman in quite a number of cases of infectious diseases of children, especially scarlet fever and diphtheria, but has been found in other infections and in adults as well. Degenerative changes in the epithelium of the tubules and glomerular changes may be slight or marked in this form of acute interstitial nephritis, so that albuminuria and cylindruria, with other ordinary urinary evidences of Bright's disease, may be very variable as to degree. The so-called "lymphomatous nephritis," with collections of cells, reminding one of multiple lymphomata, is of a somewhat similar nature, and is seen, for example, in the kidneys of typhoid fever.

The changes in *organs other than the kidney* are often those of the primary disease, *e. g.*, an acute infection. Dropsical conditions, as in the serous cavities, may be found, or there may be the lesions of some complicating affection, such as pericarditis or pleuritis. In cases of acute nephritis lasting over a few weeks hypertrophy of the left ventricle can sometimes be made out. Henschen[2] and his pupils have shown this to be true in a number of instances.

[1] *Transactions of the Association of American Physicians*, 1898, xiii, 300.
[2] *Das Herz bei Nephritis*, Jena, 1898.

Symptoms.—From the clinical point of view there are two types of acute Bright's disease. The one is characterized by an abrupt, frank onset, with œdema, pallor, headache, and gastric disturbance, and by such scantiness of urine and change in color from admixture of blood as commonly to attract the attention even of the patient or the nurse to the fact that there is something wrong. The second type is less frank in its manifestations; although the onset may be sudden, there is no marked œdema or pallor of the skin, there is no complaint of headache, no nausea or vomiting, and the urinary change is only revealed by a close watching of the amount of urine and by its chemical and microscopic study. Scarlatinal nephritis may serve as typical of the first class; the acute nephritis occurring during the course of typhoid fever or pneumonia is fairly typical of the second class.

The *frank form,* as has been said, is the one met with in scarlet fever. In many of the acute infectious diseases, especially when accompanied by high fever, a trace of albumin with a few casts can frequently be found in the urine. This is true of scarlet fever. As the fever subsides the casts and albumin disappear and the urine is practically normal. This so-called febrile albuminuria of the first few days of scarlet fever is not meant. The true scarlatinal nephritis is more apt to occur during convalescence. The temperature may have been normal for several days; desquamation is well advanced, and a complete and prompt return to health seems in sight. The child may be up and about and may have been allowed considerable freedom in the way of food. Perhaps, as the result of indiscretion in diet or of careless exposure to cold or of needless overexertion, the acute inflammation of the kidneys is excited. Yet in many cases there has been no relaxation of the vigilant care on the part of nurse or physician, the patient is still in bed, still on restricted diet, and an apparently favorable convalescence during which every known precaution against complications has been exercised, is rudely interrupted by the renal disease. Although it is, perhaps, more apt to appear following the severer attacks of scarlet fever, it is not infrequently seen after mild, even ambulatory cases.

While the order in which the symptoms make their appearance varies in different cases, and while there are many deviations from the type, as here described, it may be said that the three striking features, at least the three features that are most prominent early in the disease, are œdema, uræmic manifestations—especially headache, drowsiness, and disturbance of the stomach—and the marked change in the urine.

The *œdema* may come on with remarkable rapidity. The child's face in the morning may be seen to be puffy, the eyelids swollen, these appearances, with the obliteration of the wrinkles, the pallid, pasty color, and the watery eye, causing a peculiar apathetic, expressionless look that is quite characteristic. The same œdematous condition may be found on the backs of the hands, over the lumbar vertebræ and sacrum, constituting the "lumbar pad," and in the loose scrotal tissue. The œdema at first may be rather firm and does not pit readily. This œdema may never become extreme, but it is enough at once to attract the attention of the observant physician or nurse, especially as it is in such striking contrast to the previously normal or even emaciated appearance. In some instances it progresses and dropsical accumulations are found, not only in the legs, back, face, in fact, in all the subcutaneous tissues, but in the peritoneal, pericardial, and pleural cavities

as well, the patient presenting the waterlogged picture so commonly seen in the anasarca of chronic parenchymatous nephritis.

While dropsy in acute scarlatinal nephritis is usually quite general, it is sometimes capriciously fugitive, shifting for no assignable reason from one part of the body to another, and it will often show a tendency to shift with the position of the patient, and be most marked in the dependent portions of the body. In patients in bed it can often be detected over the lower back, when not noticeable in the extremities. In certain rare instances the fluid collects in the serous cavities to a much more marked degree than in the subcutaneous cellular tissue, the latter being entirely free from unnatural accumulations, so far as can be determined by external examination. Cases of œdema without albuminuria, following scarlet fever, are occasionally seen. They were early described by Hamilton, Phillipp, Goodak, Henoch, Bartels, and later by several others, but the correctness of the observations of Phillipp[1] of a remarkable series of sixty such cases, may be justly questioned. One such case has come under personal observation. Most of these cases resemble nephritis in all respects, although without the ordinary urinary accompaniments. Albumin and casts, in some instances, have appeared later. Autopsies in some have shown an underlying condition of nephritis.[2]

Cadet de Grassicourt reported œdema as preceding the albuminuria by three days. Brault,[3] who cites this case, emphasizes the fact that careful daily examinations of the urine of scarlatinal patients would reveal much irregularity in the order of appearance of symptoms and urinary findings. Œdema may exceptionally appear before albumin, casts and blood may precede the albumin, while in other cases albumin may be present many days before œdema is noticeable. The onset of acute nephritis may therefore be more insidious than we are accustomed to regard it, cylindruria, hæmaturia, and albuminuria, perhaps, being present for a considerable time before œdema, headache and vomiting give frank announcement of the inflammation of the kidney.

This fluid interferes more or less with the functions of various organs, *e. g.*, of the stomach and intestine, whose walls may be œdematous, or of the lungs, as when the abdominal and pleural cavities contain much of the transudate and the free play of the lungs is interfered with by the pressure of the surrounding fluid. Œdema of the glottis, fortunately comparatively rare, may be serious or even fatal. Œdema of the uvula may be annoying and extremely alarming to the patient, who is constantly harassed by the irritation in the back of the throat and by the ineffectual attempts to get rid of it by coughing or by swallowing. Some of the cerebral symptoms, such as headache and apathy, may be in part explained by cerebral œdema, the "wet brain" being often found at autopsy.

The *urine* is scanty. A few ounces only may be passed in twenty-four hours, and complete suppression may occur. There may, however, be a frequent desire to urinate and a somewhat painful vesical tenesmus may be present, only a few drops being squeezed out with each effort. The physician at times, fearing some accumulation of urine in the bladder, passes the catheter, but finds the bladder empty, or succeeds in getting

[1] Cited by Frerichs. [2] Cf. Henoch, *Berl. klin. Woch.*, 1873, No. 50.
[3] Brault in Charcot's *Traité de Médecine*, 1894, v, 680.

2 or 3 cc.; he finds it is a true renal suppression. This may continue for many hours, and still recovery be possible. The writer has known anuria to last sixty hours, in the case of a child who ultimately recovered. Rosenstein saw anuria of three days, Riegel of ten. The urine that is passed is turbid, smoky, reddish, brownish, or flesh-colored, usually acid, and deposits a heavy sediment. If the urine be alkaline, a relatively small amount of blood gives it a bright-red color (Tyson). The specific gravity of the concentrated urine is at first high, often over 1020 or even 1030. There are, however, many exceptions to this rule, for, in some instances, although the amount of urine is greatly diminished, there is such a paucity of solids as to keep the urine down to a specific gravity of 1018 or lower. Albumin is present in large amount, even to 1 per cent., or, in rare instances, more. The daily loss seldom exceeds 20 grams, although Dickinson sets 35 grams as the limit. The percentage of solids, urea, chlorides, phosphates, is increased, although the total output for twenty-four hours, owing to the scantiness of the urine, is less than normal. Bartels noted, what has lately attracted much attention in connection with the dechloridation treatment of nephritis, that the chlorides were diminished, especially in cases attended by dropsy.

The microscope shows that the sediment already referred to is made up largely of red blood corpuscles, epithelium, casts, uric acid crystals, and amorphous urates. The red cells may be well preserved or broken down into a reddish-brown, granular detritus. Shadow corpuscles are numerous. White corpuscles, and, as Senator has shown, many of the mononuclear type, are seen. Epithelial cells are abundant and casts of various kinds are found. At first blood casts and epithelial casts are especially numerous, but soon hyaline and granular forms are seen, and fatty casts, as well as waxy casts, may be met. No one form can be regarded as characteristic of an acute inflammation, although emphasis may perhaps be rightly placed on the significance of the large numbers of blood casts and epithelial casts in the earlier stages. While casts in the albuminous urine of acute nephritis may perhaps be lacking in rare instances, care should be exercised in making such a statement, for often the absence of casts is to be explained by the early decomposition of the urine, especially if collected in an unclean receptacle in hot weather. The destructive digestive action upon casts of alkaline urine, and particularly of alkaline urine full of bacteria, should be remembered before one declares that the urine of a patient is free from casts. Cases without casts are, however, occasionally recorded, as by Dickinson.

The molecular concentration of the urine is increased, as is its electric conductivity. The freezing point is, therefore, lower than normal, *i. e.*, farther removed from 0° C. The freezing point of the urine, however, is subject to wide variations. There is retention of solids, *e. g.*, urea, phosphates, and chlorides, and this retention, especially of salts like the chlorides, should bring the freezing point nearer 0° C., as it sometimes does. But there may be such concentration of the urine, owing to deficiency of water, that the freezing point may be lower than normal, *i. e.*, it may be below —2.3° C. A frequent phenomenon in disease of the kidney is the inability to pass a concentrated urine. The passage of an abnormally dilute urine occurs, constituting the hyposthenuria of Friedrich Müller.[1] Hyposthenuria is

[1] *Loc. cit.*, p. 71.

seen not alone in chronic interstitial nephritis, but also in acuter forms, especially when there is glomerular involvement, as in the form under consideration. Unless hyposthenuria be counteracted by polyuria, renal insufficiency must result. This condition is often seen early in acute nephritis, and although the urine is diminished in amount, yet it may contain but a small amount of solids, be of low specific gravity, and have a freezing point nearly that of the blood.

After what may be called the initial shock of the disease, the urine becomes somewhat more abundant, less dark and smoky colored, its percentage of albumin less, and the casts more varied in their character, although the urine is still scanty, still bloody, and still rich in albumin and casts. If recovery ensues, one of the earliest signs is an increased output of urine; polyuria may ensue, the urine becoming paler and of lower specific gravity, often much lower than normal. If œdema has been extreme and there is a rapid subsidence of it, the amount of urine as convalescence is established may be excessive and the specific gravity as low as 1010 or 1005. Dickinson reports having seen 240 ounces in twenty-four hours. The albumin and casts gradually disappear, although spasmodic outbursts of albuminuria and cylindruria may be noted, often for weeks. Johnson believed that the return of the natural color of the urine and the disappearance of the albumin occurred simultaneously, and that a practised observer might judge with some degree of accuracy from a glance at the color of the secretion as to its freedom from albumin, the urine having an unnaturally white appearance so long as the albumin continues, and recovering its usual sherry tint when it returns to its normal composition.[1] Red blood corpuscles may be found at times long after the albumin has finally disappeared (Rosenstein).

A pre-albuminuric stage of acute Bright's disease has been described by Mahomed, in which the coloring matter of the blood may be found in the urine by the Weber test with guaiacum, although red corpuscles may not be found. This observation is not generally confirmed. Rosenstein says hyaline casts are often in the urine several days before albumin.

Many of the symptoms that are now to be described are clearly of toxic, *i. e.*, *uræmic* origin. The most frequent are headache, mental apathy, nausea and vomiting. Instead of classifying certain symptoms as specifically uræmic, the phenomena are described under the heads of the various organs or systems showing derangement.

Nausea and vomiting are fairly common symptoms. They may come on so soon after the occurrence of the albuminuria and dropsy as to raise the question of their uræmic origin; they are at times so nearly coincident with the retention of urine as to make one think of the existence of a toxin producing at the same time the lesion in the kidney and the disturbance of the stomach, perhaps through its nervous mechanism, rather than a retention toxæmia through faulty elimination attending urinary suppression. In other cases—in most cases—there is a rather close relation between the amount of urine secreted and the severity of the gastric disturbance. Within the first few days, when perhaps less than five or six ounces are passed, there is complete anorexia, nausea, and prompt rejection of food, drink, or medicine that may be put into the stomach. The tongue becomes coated and dry; stomatitis resembling that of scurvy has been described. There

[1] G. Johnson, *Diseases of the Kidney*, 1852, p. 87.

is a fœtid odor to the breath, at times suggestive of urine. This urinous odor may be detected in the vomitus. The bowels may be constipated or loose, diarrhœa being oftener a late than an early manifestation. Vicarious elimination through the stomach and bowel is regarded by many as an explanation of the vomiting and the diarrhœa, the urinous odor of the vomitus being held to be due to urinous constituents eliminated by way of the mucous membranes of the stomach perhaps after they have been converted into ammonia or ammoniacal salts. Senator believes the peculiar odor to the breath as well as to the stomach contents is due to trimethylamin.

There is rarely much *fever*. Occasionally an initial chill or chilliness will be followed by quite a sharp rise to 102°, or even more. Oftener the temperature even at the onset will be less than 100°, or even normal. It is not correct, however, to regard acute nephritis as an afebrile disease, for, in many cases, careful observations will show a slight rise. The fever rarely lasts more than a few days, unless inflammatory complications or uræmic convulsions with coma occur. Leube[1] saw no case of nephritis with fever during an entire decade, and then saw several in succession that were febrile.

The *pulse* increases in rapidity and often even quite early has a hard, high-tension quality, showing a rise in blood pressure. In other cases a slow pulse may be present throughout. In fact, some regard bradycardia as quite characteristic of acute Bright's disease. Often even by the end of a month a definite enlargement of the *left ventricle* can be made out, and with the loudness of the first apical tone and the sharpness of the aortic second, make it clear that the vascular tension is high, a fact readily confirmed by the sphygmomanometer. Dilatation may occur at any time. These cardiovascular changes, however, are not to be detected in all cases, although a sharp aortic closure is common. Friedländer found the heart at some autopsies on scarlatinal nephritis to be increased 50 per cent. in weight, yet often there was no increase. As convalescence ensues, the pulse may become quite slow and intermittent or even irregular. Permanent cardiac derangement after acute nephritis is rare, unless infectious cardiac complications have occurred. Occasionally one sees a moderately hypertrophied heart in adult life, where from the history one would suspect an acute nephritic origin.[2]

The causes of the cardiovascular changes in nephritis will be elsewhere discussed. Summarized, the theories that apply in acute nephritis are (1) obstruction to renal capillary circulation (glomerulonephritis). (2) Irritation from chemical substances in the blood, acting on the heart itself, causing constriction of peripheral vessels, with rise in blood pressure. (3) Increased volume of blood, *i. e.*, hydræmic plethora.

The *skin* is dry. If œdema is excessive, it may be glossy and looks unnaturally thin and transparent. Pruritus may lead to scratching and infection; the traumatic lesions produced in this way may cause local or quite diffuse inflammation of the skin and subcutaneous tissue, or genuine erysipelas. Papular and erythematous eruptions sometimes occur, presumably to be classed under the head of the toxic dermatoses. A few times with uræmia a white frost-like deposit of urea has appeared on the skin.

[1] *Diagnostik der inneren Krankheiten*, 1895, i, 322.

[2] On the cardiac changes in acute nephritis, see Henschen, *Ueber das Herz bei Nephritis*, Jena, 1898.

The *blood* is that of secondary anæmia, the reduction in hæmoglobin being more marked than that of the red corpuscles. The anæmia in many cases is more apparent than real, the seeming loss in erythrocytes and hæmoglobin being due to the increase in the water of the blood, which is therefore diluted or hydræmic. The specific gravity of the serum is stated by Christison to be as low at times as 1019, instead of the normal 1030. But a real blood deterioration takes place in all cases of longer standing, as is seen in those patients who during convalescence, when œdema and albuminuria have disappeared, are still found decidedly anæmic. The pallid, pasty appearance of acute nephritis is due, in part, therefore, to a genuine loss in erythrocytes and hæmoglobin, but also to a thinning of the blood in the vessels, and to the spreading out of the capillary vessels over an increased area, caused by the œdematous swelling. The molecular concentration tends to be increased, but there are great modifications of this rule, as also in the case of molecular concentration of the urine. An increase in œdema or of anæmia generally lessens the molecular concentration of the blood, and the freezing point under these circumstances may be normal, —0.56° C. or even less than this, *e. g.*, —0.54° C.

Hemorrhages are relatively rare in acute nephritis, although nosebleed is sometimes seen and occasionally hemorrhages in the retina are noted. In the cases with purpuric manifestations to which reference has been made in discussing the etiology, the renal condition appears to be secondary, the purpuric lesions or the erythematous nodes distinctly antedating the albuminuria. A scorbutic-like stomatitis and gingivitis have already been mentioned.

Respiratory symptoms are usually due to a bronchitis or to œdema of the lungs and bronchi. Œdema of the lungs in nephritis is, however, quite often cardiac in its origin, although primarily to be ascribed to the kidney, whose inflammation is the cause of the cardiac incompetency. The combination of bronchitis and pulmonary œdema may result in what has been termed "serous pneumonia." True lobar pneumonia is rare as a complication, bronchopneumonia somewhat more frequent. Dyspnœa may be uræmic or cardiac in origin, due to the extensive bronchitis and œdema, or may depend largely on the presence and pressure of accumulations of fluid in the pericardial, pleural, or peritoneal sacs. True intercurrent pleurisy is not so very rare. Cheyne-Stokes breathing is often a manifestation of uræmia. Asthmatic attacks are apparently at times uræmic or at times cardiac in character.

Headache is frequently an early evidence of nephritis. As uræmic intoxication becomes more pronounced, it may be a most distressing, almost unbearable, condition. Dizziness and tinnitus may be other manifestations. Not a few patients grow apathetic, drowsy, even stuporous, or comatose, without convulsions. The mind may be clouded and delirium of a low and muttering type or of a wilder character may manifest itself. *Amaurosis* and retinitis are rare as compared to their frequency in chronic interstitial nephritis, although they are occasionally seen. Uræmic deafness is rare, although met with. *Uræmic palsies*, also, while occurring, are infrequent as compared to their frequency in chronic nephritis. Amaurosis, retinitis, and palsies are more apt to occur in the acute cases that have lasted some time and that might be said to be in the subacute stage.

Convulsions rarely occur until the condition has lasted for several days or weeks. They are of the epileptiform character, and are usually preceded

and in a sense heralded by severe headache, vomiting, epigastric pain, with increase in pulse tension, and perhaps muscular twitchings. Coma may follow the attack, and is particularly apt to supervene on several attacks that follow one another in rapid succession. In some cases the torpor and drowsiness may pass into a coma, perhaps fatal, without there being any convulsion. These cases are more often those in which an early nearly complete suppression of urine has occurred. They resemble in some respects more the toxæmia of anuria than that of true uræmia, as seen in cases of several weeks' standing.[1]

General *malaise*, with more or less aching in the limbs, is apt to be present, particularly when there is much fever at the beginning. There is often pain in the back, of a dull aching character. At times it may be severe enough to justify Basham's description of an "urgent aching pain across the loins." It is rarely severe, however, and has none of the characteristics of the pain of renal colic. Rayer's observation that he had never in acute nephritis seen a retraction of the testicle or the radiation of pain along the ureters has been generally confirmed. Even the passage of blood in the shape of clots is so rare that pain from this cause partaking of the character of ureteral colicky pain is almost never noticed. There may be some tenderness on pressure in the loins over the region of the kidney. Vesical tenesmus with some slight urethral burning during micturition may be annoying, but is seldom very painful. Concentration of the urine may explain in part, at least, the frequent and burning micturition. There is sometimes complaint of pain in the epigastrium, aside from the uneasiness and discomfort attending the nausea and vomiting. Headache may occur early, and may be severe. If the brusque symptoms of the initial period pass away, headache is apt to lessen, at least temporarily, but the onset of later uræmic convulsions may be heralded by a recurrence of severe headache.

Nephritis from Cold; Nephritis a Frigore.—While one can hardly agree with Rayer or Stewart when they say that the most common cause of inflammation of the kidney is exposure to cold and wet, one must admit that at times a very definite influence of cold is seen in producing acute Bright's disease. Lassar's experiments on lower animals seem to show the positive influence of cold in this direction. It is apparently not so much cold alone as prolonged or repeated exposure to cold and wet, coupled with exhaustion, starvation, and the excessive use of alcohol.

Clinically, nephritis of this type resembles very closely the type seen in scarlet fever. The onset is usually abrupt, the œdema frankly generalized and the urine rich in albumin, casts, and blood. Chilliness, with some rise of temperature, may be present, and there is a dull pain in the loins. Lecorché claims to be able by palpation to make out an increase in size of the kidney. This is certainly exceptional. Uræmic headache, apathy, nausea, convulsions, or coma may or may not be pronounced. Some of the cases are more insidious in onset, and in their long-drawn-out course might be classed as subacute or even be said to merge imperceptibly into the chronic parenchymatous form. Recovery from acute nephritis due to cold is the rule, although it is often a matter of many weeks or even months. Bartels saw a recovery after a duration of one year.

[1] For a good discussion of the differences between uræmic and anuric intoxication phenomena, see Ascoli, *Die Uræmie*, 1903, p. 144 et seq.

Alcoholic excess is a factor in the production of both acute and chronic nephritis. Strümpell describes cases as occurring in the heavy beer drinkers of Bavaria, particularly in the obese and after exposure to cold. The œdema in these cases was pronounced, and made its appearance rapidly; the urine was scanty and heavily albuminous, while casts were plentiful; blood was absent, and the urine was not smoky or even turbid. In the instances in which alcohol appears to be the exciting cause there is commonly a history of a definite, usually prolonged period of excessive drinking rather than of habitual indulgence; or some debilitating condition, such as tuberculosis, heart disease, or anæmia, has already been present. The onset is often rather insidious than outspokenly active, and the course of the disease borders on the subacute or chronic parenchymatous, the cardiovascular changes not being a striking feature.

In many of the infectious diseases, as has been said, there is a form of nephritis differing in its clinical behavior from that met with in scarlet fever. The difference is seen in the more insidious onset, the lack of œdema or its comparatively slow and only slight development, in the absence of pronounced headache, nausea, and vomiting, and in the rarity of marked hæmaturia and scantiness of urine. In many of these cases, too, the symptoms of nephritis are lost in those of the primary disease that is still at its height, and they do not stand out prominently against the background of symptomless convalescence as in scarlet fever. While the symptoms of acute nephritis as it occurs in connection with a given infectious disease are not so pathognomonic as to enable one from the clinical manifestations alone to recognize the organism that is at fault, there are yet certain features which are rather characteristic. It is possible that in the future the clinical diagnosis will be more accurately made, as the lines of differentiation between forms etiologically distinct are more sharply drawn. Even at the risk of repeating some things already said under the head of etiology, an outline of facts will be given concerning some of these varieties of acute nephritis.

By this form of acute nephritis is meant something different from the so-called *febrile albuminuria* that is so commonly seen in most acute infections. This trace of albumin with an occasional cast or red blood corpuscle is without accompanying clinical symptoms that can rightly be ascribed to renal change, and is due to the acute degeneration of the renal parenchyma—the cloudy swelling. Some, of course, regard this as inflammatory, and speak of this condition as a tubal nephritis, as often an initial stage of a more pronounced exudative inflammation. But, clinically, quite a sharp line must be drawn between this condition which is coincident with the existence of the fever, and the form that may occur either at a time when the fever is present or has passed. This is accompanied by symptoms due to defective renal function, and by characteristic urinary findings; its existence usually long outlasts the duration of the primary specific infectious disease.

In *typhoid fever*, acute nephritis may be an early occurrence, constituting the so-called *renal typhoid*. The albumin, cylinders, and blood in the urine, the temperature, gastric disturbance, headache, and mental apathy may all seem dependent on the nephritis, and the infection with the typhoid bacillus may not be recognized until rose spots, enlarged spleen, positive Widal test, or cultivation of the germs from the blood make it clear that the nephritis was but an early result of the typhoid infection.

More commonly the inflammation of the kidneys occurs during the height of the fever or just as convalescence seems in sight. There is rarely any appreciable increase in temperature, or complaint of pain on the part of the patient. Œdema is commonly lacking or is very slight indeed. It is only by the frequent routine examination of the urine that the existence of the complication is recognized. Albumin and casts are abundant; blood is present in varying quantities. These urinary findings may last for from several days to many months. Rosenstein quotes the history of such a patient, in whom there was first the ordinary febrile albuminuria, then as convalescence was approaching, the occurrence of the typical urinary findings of acute nephritis, very slight œdema, some hydrothorax, with recovery after six months. In such cases the outlook for recovery is generally fairly good, although there is not only the original disease to contend against, but there is the added danger of uræmia and such complications as pneumonia or serositis. Chronic nephritis is believed to have its origin occasionally in such cases, and it is possible that overlooked nephritis, not only during typhoid fever, but during other acute infections, may be the explanation of not a few cases of chronic Bright's disease of obscure origin.

Diphtheria so commonly produces a trace of albumin in the urine that before the days of the Klebs-Loeffler bacillus and reliance upon its detection in the faucial exudate as a means of diagnosis, the albuminuria—febrile albuminuria—was looked upon as of considerable value, and as favoring a diagnosis of diphtheria rather than a simple tonsillitis. A true acute nephritis is by no means a rarity in diphtheria. Occurring early during the height of the disease, or as the fever is subsiding, it is manifest by the diminished urine, that, while perhaps clear and only slightly discolored from blood, is yet richly albuminous, often even richer than in scarlatinal nephritis. Casts and renal epithelium are present in abundance. Œdema is absent or is mild in degree. Uræmia may be slight or more rarely severe. Recovery is the rule. Diphtheric nephritis is usually tubular.

Febrile albuminuria is found in nearly every case of *croupous pneumonia* when careful search is made. A few casts can also be found. True nephritis is found in 1.7 per cent. of cases (Rosenstein). It lasts for a few to many weeks, and usually ends in recovery. The examination of the urine is usually the only means of making a diagnosis, as the frequent lack of œdema, of frank uræmic symptoms, and of increase in blood pressure gives no hint of the existence of a renal complication. It is easy to mistake an acute exacerbation of a chronic nephritis, or a previously existing acute nephritis complicated by a pneumonia, for a nephritis excited by the pneumonia unless the prior condition of the patient is known or can be elicited from the history.

Accompanying influenza or in the postfebrile period after *influenza* an acute nephritis with albumin, casts, and blood may be seen. Œdema may or may not occur. Blood pressure is slightly increased. Recovery is the rule, although in some instances there are for a time marked oliguria, renal insufficiency, and resulting toxic symptoms that may prove fatal.

Of the eruptive diseases besides scarlet fever, *typhus fever* and *smallpox* are the ones most likely to have complicating acute nephritis. It may appear in variola at any stage of the disease. Some of the cases seen in the stage of pustulation are probably cases due to some other microörganism than that of smallpox, *i. e.*, to a secondarily infecting germ, *e. g.*, the streptococcus or staphylococcus. *Varicella* is very rarely a cause of nephritis. *Vaccination*

is occasionally blamed for a nephritis, but apparently only when some pyogenic germ accidentally gains entrance through the vaccination wound can vaccinia be regarded as the cause of Bright's disease. A certain number of cases have followed *measles*, although the number is small when compared to scarlet fever. Kahlden is quoted by Freytag as saying that in the nephritis of measles albumin may be lacking, although the other abnormal constituents of the urine, the œdema and the uræmia, may be present.

Reference has already been made to the causal influence of *malaria* in the production of nephritis. Albuminuria without other evidence of renal involvement is very common during or soon after a malarial paroxysm. In the true acute nephritis œdema is the rule. Albumin and casts are abundant, and there is usually considerable blood. While most of the patients recover, fatalities may result or a chronic nephritis may follow.

Acute nephritis in the course of *erysipelas* is recognized by the ordinary urinary findings. Recovery is the rule.

In *rheumatic fever* acute nephritis is rare, although in the *purpuras*, often classed as rheumatic, it is sometimes seen with marked œdema, hæmaturia, and uræmia, and is a most serious complication. The acute rheumatic endocarditis is rarely accompained by nephritis. The same cannot, however, be said of the *ulcerative endocarditis*, during which, as during *septicæmia* unaccompanied by endocarditis, an acute inflammation of the kidneys may be lighted up and run a virulent course. Embolic nephritis in the course of ulcerative endocarditis is often seen accompanied by blood, albumin, casts, and often attended by definite lumbar pain. Some cases of acute nephritis occurring during sepsis are followed by chronic indurative nephritis, a sequence the more easily understood when one considers that in streptococcus and pneumococcus infections interstitial changes are especially pronounced. With acute staphylococcus infections epithelial degenerations are said to be commoner.[1] Blood pressure may be low.

The acute nephritis occurring during the course of *pulmonary tuberculosis* may or may not be accompanied by œdema and by blood in the urine. Many of these cases are on the borderline of the chronic parenchymatous form and show diminished urine, albumin, casts, and œdema. Amyloid changes in the kidney may cause a picture resembling that of acute Bright's disease. Such an acute nephritis is always a serious complication in tuberculosis, and often hastens a fatal termination. Uræmia and cardiovascular changes are unusual. In the nephritis accompanying tuberculosis the heart is apparently normal in nearly all cases.[2] Senator and Müller find this same lack of cardiac hypertrophy.

In *Asiatic cholera* there is oliguria. In severer cases there is anuria which may last for hours or days. What urine is passed is concentrated and contains an abundance of renal epithelial cells in various stages of degeneration, and often some albumin and a few casts. In some cases of cholera the urine is heavily albuminous and contains large numbers of casts, red blood corpuscles, epithelial cells and debris. Indican and diacetic acid may be present. This form of nephritis is believed to be a strong contributory factor in the causation of the headache, convulsions, coma, and death that often follow at the end of a few days. Dropsy is rare. Recovery after anuria of seven

[1] Müller, *loc. cit.*, p. 94.
[2] Walsh in *Third Annual Report of the Henry Phipps Institute*, 1905–1906, p. 357.

days is exceptional. The kidneys in cholera are reddish or bluish red in color, and show an intense congestion. The chief change is a marked degeneration of the tubular epithelium, nuclei and cell body often being represented by granular detritus, which with casts and blood corpuscles may be found in the tubules. Even in cholera patients who die within a few hours from the onset of choleraic symptoms distinct degenerative changes are to be noted in the epithelium of the convoluted tubules. The glomerular changes consist chiefly in extreme engorgement of the capillaries. The renal changes are probably toxic in origin, although the influence of loss of water with resulting concentration of the blood and of venous stasis from extremely weak heart action are factors that must enter largely into the causation of choleraic nephritis.

Bamberger, Litten, Aufrecht, and others have described a *primary acute nephritis*. Strümpell also refers to it. It is frank in onset, with chilliness, some fever, pain in the back or in the extremities, headache, nausea, and œdema. The spleen is said at times to be enlarged. The urine is scanty and contains albumin, casts, and blood. After days or weeks recovery usually ensues, although occasionally death or a chronic form of Bright's disease results. For this so-called primary or idiopathic nephritis no cause is discoverable. Presumably some unrecognized infection or intoxication will explain the majority of the cases. The history is sometimes suggestive of such an origin, showing a preceding sore throat, catching cold, or supposedly trifling febrile disturbance.

The relation of *syphilis* to acute nephritis has already been discussed. Albumin and casts with or without œdema give the clue to the diagnosis. Mercury is regarded as occasionally causing it.

The Kidney of Pregnancy.—During pregnancy renal changes are often met with that are accompanied, as a rule, by abnormal urinary findings, and at times by recognizable clinical symptoms. These lesions of the kidney, because of certain anatomical peculiarities, of the uncertainty as to their inflammatory nature, and because of the atypical accompanying clinical manifestations, are not generally classed as nephritic. The tendency to-day is to speak of this kidney as the "kidney of pregnancy." It is to be remembered that the woman already the possessor of an inflamed kidney may become pregnant as well as that the pregnant woman may have acute Bright's disease. An already existing, although previously unsuspected, nephritis is liable to become aggravated under the influence of pregnancy. These instances of true nephritis with or without uræmia are not to be classed with the so-called kidney of pregnancy.

Anatomically, such a kidney is increased in size. Its color is often lighter than normal. In consistency it is somewhat soft. The changes are almost entirely in the convoluted tubules of the cortex; interstitial changes are absent; those in the glomerulus are generally slight. Virchow pointed out fat emboli in the glomerular vessels. The renal epithelial cells are swollen and distorted, filled with fine granules and show varying degrees of fatty degeneration. It is largely owing to this fatty change that the light color of the organ is due. Sometimes the cells show extensive necrosis; this is often irregularly distributed throughout the kidney, *i. e.*, patchy. Casts may be seen in the tubules, especially those of the medullary portion, in which position the parenchymatous changes already described are generally but slightly advanced.

The explanations offered for the origin of the kidney of pregnancy are varied and in a measure largely speculative. They may be conveniently classed as (*a*) mechanical, *i. e.*, pressure; (*b*) toxic; (*c*) bacterial; (*d*) a combination of these three causes.

That there is *pressure* upon the ureters, the renal vessels, and even upon the kidney itself is shown by numerous autopsy findings. The greater tendency of this particular lesion of the kidney to appear in primiparæ is explained by many as due to the greater frequency of those conditions that would favor an increase of pressure, viz., twin pregnancy, hydramnios, contracted pelvis, and firm unyielding abdominal walls.[1] The occurrence of eclampsia after the emptying of the uterus and the apparent removal of the cause of pressure may, perhaps, be explained on this theory, as suggested by Webster,[2] by the plugging of the pelvic opening for two or three days' postpartum by the still large uterus. His frozen sections showed the possibility of ureteral pressure from this cause.

The *toxic* theory first brought prominently forward by Virchow,[3] in 1848, explains the lesions in the kidney as due to the irritation of the renal cells by toxins in the blood, the result of increased, perhaps faulty, metabolism, with poor elimination. The mother has not only to provide for the proper performance of the complete metabolic process for herself, including elimination, but for the fetus—sometimes two fetuses—as well. The prejudice of even the civilized pregnant woman against ordinary cleanliness of the skin because of fear of catching cold, her aversion to exercise particularly in the later months of pregnancy, and especially in the open air, the frequent obstinate constipation, the faulty performance of function on the part of the stomach, sluggish action of the kidneys—these are some of the explanations offered for the accumulation of an undue amount of toxic material in the blood of the pregnant woman, which substance may harm the delicate renal parenchyma.

Bacteria have not been found with enough uniformity in these cases to make one feel that they play any very important role in the causation of this condition, although bacterial invasion of the blood or unusual bacterial activity in the alimentary tract might easily be conceived of as contributing to the condition of toxæmia.

One is perhaps justified in regarding the renal changes that resemble those of degeneration as chiefly due to toxic conditions, although the influence of mechanical obstruction to the ureters or the renal vessels in interfering with the nourishment of the renal cells, and with their function of elimination is certainly not to be overlooked.

The clinical manifestations vary from a trace of albumin, with a few casts, in the urine, but no subjective symptoms of toxæmia—a condition that is regarded by many as rather physiological than pathological, especially in the last weeks of pregnancy—to a heavily albuminous urine, containing casts and blood, and subjective symptoms suggestive of most profound toxæmia, and culminating oftentimes in an eclamptic explosion. The urine, when this condition is at all advanced, is usually somewhat scanty, turbid, the specific gravity averaging higher than normal. Albumin is present and may be excessive in amount. Casts generally of the hyaline or granular varieties are

[1] Halbertsma, *Centralbl. f. d. med. Wissenschaft*, 1871, No. 27.
[2] *Text-book of Obstetrics*, p. 314. [3] *Gesammelte Abhandlungen*, 1856, p. 778.

present, as well as some red blood corpuscles, a few leukocytes, and renal epithelium in various stages of degeneration.

Œdema is common not only in the dependent portions of the body, as the legs, where pressure on the return circulation might in a measure account for it, but in the face, the hands, the back. Sometimes a pallor gives the patient the pasty look seen in typical cases of parenchymatous nephritis. Symptoms of toxæmia are more or less pronounced and resemble those commonly described as uræmic. Among these may be mentioned headache, dizziness, sleeplessness, apathy, dimness of vision amounting at times to amaurosis, nausea and vomiting, epigastric uneasiness or even severe pain, unusual dyspnœa, perhaps diarrhœa or obstinate constipation. These may be the forerunners of an epileptiform seizure, occurring in the later months of pregnancy, during labor, or in the first few days thereafter. If the condition reaches the stage of eclampsia, the outlook is extremely serious for both mother and fetus, about 25 per cent. of the mothers dying, and a larger percentage of the children. If the attack passes away, recovery may ensue promptly, the urine rapidly clearing and the unpleasant symptoms vanishing. Aufrecht had a patient in whom after eclampsia the urine promptly became normal, and, the patient dying from another cause within five days, the kidneys were found in this short time to have undergone complete restoration, no pathological lesion being demonstrable.

The *diagnosis* of the kidney of pregnancy is usually a simple matter if the physician have knowledge of the condition of the urine at the beginning of pregnancy. Otherwise, he must consider whether he is dealing with a renal congestion, a chronic nephritis with the added element of congestion, or an acute nephritis. A positive diagnosis is at times impossible. Simple congestion rarely gives the large amount of albumin found in the urine of the kidney of pregnancy, nor does it cause the generalized œdema or the marked toxic symptoms of that condition. Of great help in the diagnosis of an old nephritis is the finding of typical cardiovascular changes, and of ancient albuminuric retinitis, as well as a history of nocturnal pollakiuria and polyuria before pregnancy. An acute nephritis may be impossible to differentiate from the kidney of pregnancy, although especially liable to have more blood and more casts and to be attributable to some acute infectious process. The urine in either the acute or chronic nephritis will not, of course, clear up as promptly on emptying the uterus, as in the case of the kidney of pregnancy, nor do the toxic symptoms subside as rapidly.

The *prognosis*, except when eclampsia occurs, is not serious. If eclampsia occurs, the mortality of the mother is about 25 per cent.; for the child still greater.

The *treatment* of the kidney of pregnancy and the nature and treatment of puerperal eclampsia are matters for discussion in a text-book on obstetrics, yet a brief word may be here said on the subject of therapy. Too great caution cannot be observed in watching for the appearance of albumin and casts in the urine of the pregnant woman, and for the occurrence of œdema of the face and hands, headache, unusual dizziness, blindness, epigastric pain, etc. These things should be viewed with suspicion, as possibly indicating the existence of the kidney of pregnancy with impending eclampsia. Especial care should be exercised in the case of the woman who may have had eclampsia in some previous pregnancy. It is to be remembered, too, that occasionally eclamptic seizures have occurred in the non-albuminuric

pregnant woman, so that the before-mentioned toxæmic symptoms should be regarded as notes of warning, even although no albumin be present. For the eclampsia, sedatives, such as bromides, chloral, and chloroform, should be employed; bleeding may be of benefit, and saline infusions may help to dilute and wash out the toxine. The uterus should be promptly emptied. When before eclampsia the urinary findings show no sign of improvement and the toxæmic symptoms are increasing in severity, it would seem to be the part of wisdom to empty the uterus at once rather than to run the risk of having the dreaded eclamptic complication at the time of labor.

In general, the treatment of the kidney of pregnancy is that of acute nephritis; the same hygienic and dietetic precautions, the avoidance of over-exertion, a goodly amount of rest, daily warm baths, and as free elimination as possible through the bowel, skin, and kidney.

Complications.—Acute nephritis, like the other forms of inflammation of the kidney, is likely to be complicated by other diseases. Among these must be mentioned bronchitis, that may lead to a bronchopneumonia. True croupous pneumonia is not so very uncommon, and its course is apt to be rapid. It may be readily overlooked, unless careful physical examination be made, for bronchial cough, dyspnœa from uræmia or from cardiac causes, or perhaps from hydrothorax, may obscure symptoms by offering a plausible explanation for respiratory manifestations otherwise quickly attracting attention as possibly indicative of pneumonia. Œdema of the chest wall, fluid in the pleural sacs or pericardium, and bronchial rales often make physical exploration for pneumonic consolidation quite difficult. Any unusual increase in respiration rate or any unusual dyspnœa or cough, especially if the latter be attended by rusty sputum, should lead to careful examination of the chest, as should otherwise unaccountable rise in pulse rate or in temperature. The upper lobe is said to be very frequently the one involved in acute nephritis. By some a form regarded as a "lobar non-croupous pneumonia," a serous pneumonia (Fürbringer), is to be distinguished from the ordinary complicating croupous pneumonia. While one is seldom in doubt as to which disease is the primary one, occasionally when the early history of the case is lacking, as often happens in hospital practice, the question as to whether, for example, a pneumonia has given rise to an acute nephritis or the nephritis has been complicated by a pneumonia, is not an easy one to decide.

The great frequency with which the pleura, pericardium, and peritoneum show inflammation during acute nephritis is well known. Daily examination is necessary in order to detect these complications, and even slight pain and tenderness should receive careful consideration. Other complications or intercurrent troubles may, of course, occur, such as meningitis or erysipelas. Œdema of the glottis is a serious manifestation which might be classed as a complication.

Diagnosis.—The diagnosis of acute nephritis presents little difficulty if the physician is familiar with the condition of the patient before the onset of the renal disease; the sudden appearance of the characteristic urinary findings leaves little or no doubt as to the nature of the trouble. When one has no knowledge of the previous condition of the kidney there may be often a question as to diagnosis. Among the conditions most liable to cause confusion are cyclic albuminuria, febrile albuminuria, congestion, acute exacerbation of a chronic nephritis, chronic parenchymatous nephritis, amyloid kidney, infarct, and more rarely such conditions as tuberculosis,

tumor, calculus, pyelitis, etc. The main points in the differentiation may be briefly stated as follows:

Cyclic albuminuria, or the albuminuria of adolescence, is seen in the young, unaccompanied by œdema, cardiovascular changes, or uræmia. The urine shows no blood, only occasionally casts, the albumin is not constant, is usually rather small in amount, and is especially apt to be noted after a heavy meal, after exertion, or after the patient has been on her feet for a time (orthostatic albuminuria).

Febrile albuminuria is seen during the acute infections accompanied by fever. The albumin is but a trace, casts and blood are not abundant; there is no œdema or uræmia. No increase in blood pressure that could be attributed to renal disease is made out. There are cases, however, as has been said, in which it is difficult to draw a sharp line between a marked febrile albuminuria and a mild grade of acute nephritis. And, as is known, some consider even these cases of febrile albuminuria—acute parenchymatous degeneration—as inflammatory in character and as representing a mild or perhaps initial stage of true inflammation.

In *congestion* of the kidney a cause is seen as in a non-compensated cardiac disease or other condition lowering arterial pressure. Dyspnœa, congestion of the liver, and œdema of the lower extremities, with other evidences of cardiac incompetence may show the existence of such a cause. The general anasarca of nephritis involving face, hands, etc., is not present. The urine is concentrated, but contains what for acute nephritis would be a small amount of albumin and a small number of casts. The therapeutic test is often of great value; rest in bed with treatment directed to the cause, *e. g.*, the heart, if successful in overcoming such cause, will result in a prompt return to normal conditions in the urine.

Chronic parenchymatous nephritis and the acute form run imperceptibly into each other. Unless we know the definite history from the beginning, showing an abrupt onset, a causal relation to an acute infection or acute intoxication, the early urinary suppression, hæmaturia, etc., a definite differential diagnosis may be impossible until careful watching and time enable one to determine the essentially chronic character of the disease.

A condition that is very common and one that frequently causes confusion as to diagnosis is a chronic diffuse or interstitial nephritis, on which there is engrafted an acute inflammation. The existence of the chronic trouble may have been unknown to either patient or physician. The acute onset, œdema, headache, nausea, etc., call attention to the kidney, and the urine, richly albuminous and containing numerous casts and blood corpuscles, resembles that of an acute nephritis. Suspicion as to the previous existence of a chronic disease should be aroused by a history of polyuria—especially nocturnal—headache, dyspnœa, gastric disturbances, etc. When on examination typical cardiovascular changes are found, more marked than could be accounted for by an acute nephritis of only a few days' duration, or when an old albuminuric retinitis is found, there is strong ground for believing that the acute process has been lighted up on the basis of an old affair. It often happens, too, in cases of this kind, that a study of the twenty-four hours' urine will show an amount somewhat above the normal, a specific gravity a little low—say 1012—while the albumin, blood, and casts are abundant. In other words, the urine has certain characteristics—amount and gravity—like those of chronic interstitial nephritis, while in other respects it resembles the acute.

Prognosis and Termination.—Acute nephritis is always a serious disease. Yet it has a natural tendency toward recovery, and in the great majority of cases—the exact percentage it is impossible to state—a recovery ensues that seems to indicate a complete restoration of function on the part of the kidney, although some are inclined to look upon such a kidney as thereafter peculiarly vulnerable and especially liable to be again involved in a recurring inflammation. Early relapses or, more strictly, exacerbations of the acute nephritis are not so unusual, and should make one guarded in his statements as to outcome until the urinary and other evidences of the disease are well out of the way. The length of time that must ensue before recovery occurs varies greatly. One month is a short time. Yet even after six months, a year, or exceptionally even longer, recovery may take place. Cabot's collective study of this question is instructive.

Aside from recovery, a pseudorecovery and what by the laity and the careless physician may pass for a recovery is occasionally seen, viz., the passage of the acute into the chronic form without œdema. This is not a very common occurrence, but the fact that it does occur should lead to the examination of the patient at intervals after the subsidence of the symptoms of the acute Bright's disease, to see whether evidence of the chronic diffuse form or of the so-called secondary contracting kidney is to be found in the urine or cardiovascular system. Rayer[1] gives a very graphic description of these cases of supposed recovery which lull the unsuspecting patient and the easy-going physician into a false feeling of security, and which in later years show evidence of the long-standing existence of the renal disease that has been overlooked, by perhaps a sudden uræmic explosion, or by an acute exacerbation with dropsy and other familiar signs.

Death in acute nephritis may occur in a variety of ways. Uræmia is a common cause, with convulsions or coma, or perhaps indirectly through the exhaustion it brings about by loss of sleep, anorexia, vomiting, diarrhœa, anæmia, etc. Anuria may be the cause. In some instances there is an abrupt, nearly complete, or quite complete suppression of urine. This may last for a few days and not cause death, but unless the urinary elimination be reëstablished, death from anuria follows, and this happens in a certain proportion of cases. The complications already mentioned may be the cause of death. Dickinson says that while in those over sixteen uræmia is the common cause of death, in those under that age the cause in 50 per cent. is inflammation of the respiratory tract, uræmia taking second place. Œdema may contribute largely to bring about the fatal result, and, as in œdema of the glottis, may be the immediate cause of death. Cerebral hemorrhage is a rare cause of death, as compared to its frequency in the chronic forms. Occasionally an acute anæmia from severe nosebleed, or hemorrhage from the stomach or bowel, will have a decided influence in causing death. Cardiac weakness and dilatation, sometimes sudden, may also be fatal. And, as stated, death may be long deferred and occur as the result of the secondary chronic form of the disease.

No definite data as to how to make a prognosis in a given case can be given. Each case must be studied on its own merits and an estimate made as carefully as one can of the general tendency of the disease, as shown by urinary findings, the progress of toxic symptoms, of œdema, and cardiovascular changes. Some help may come, at least in predicting uræmia, from a cryo-

[1] *Traité des Maladies des Reins*, 1839, vol. ii, p. 112.

scopic study of the urine and blood, as well as from watching for a rise in blood pressure which often precedes uræmia. Various criteria on which to base a prognosis are given by different authors, but in reality one must judge each case on its merits and still feel, even after a careful weighing of all facts, that it is a very difficult and uncertain matter to forecast the future in acute Bright's disease. Bartels, for example, says that every case with complete suppression is fatal, but exceptions to this occur, as the writer can testify from personal observation. Fürbringer regards the prognosis as especially bad when the urinary sediment is rich in lymph corpuscles. Dickinson thinks the total absence of blood in the urine is not a good sign, as bleeding relieves the organ. He also says that the majority of fatal cases die inside of six months. Other prognostic aids might be cited, but they are quite unreliable.

Treatment.—**Prophylaxis.**—Just how much may be accomplished in the way of preventing acute nephritis in a given patient it is difficult to say. Yet undoubtedly the disease is often warded off by care in lessening or removing the influence of causes that are liable to produce acute inflammation of the kidney. Roughly speaking, the proper treatment of any acute infection may be regarded as prophylactic against disease of the kidney. The early and efficient use of antitoxin in diphtheria, or of quinine in malaria, will lessen the danger of nephritis. Simple sore throats deserve treatment because of the possibility of their being the starting point of visceral complications including nephritis. And so care in every acute infection and, unless otherwise contra-indicated, the free use of water as a diluent and eliminant, and attention to catharsis, may be the means of sparing the kidney undue irritation, and in this way may avoid nephritis. There are no special rules to be given concerning the management of scarlet fever; there is surely no certainty that the milder case will not manifest the renal complication. But knowing the remarkable tendency for this complication to appear during convalescence, not only should most careful attention be given the patient during the height of the disease, but precautions as to diet, clothing, exercise, use of drugs, catharsis, etc., should extend well into the period of convalescence. Whether Mahomed is right in thinking that the onset of nephritis in scarlet fever is heralded by a rise in blood pressure and the appearance of blood coloring matter in the urine, there should be most careful daily watching, and lessened total output, traces of albumin or of blood, or a few casts should be a hint for unusual care.

How far the external use of water may influence the kidneys is still a matter not definitely settled. Warm or tepid baths, sponge baths, or packs, when combined with the free drinking of water, are surely not harmful. The cold sponge or the cold bath or tubbing, as in the Brand treatment of typhoid fever, is feared by some as possibly inducing congestion of the kidney, that may be the forerunner of a genuine inflammation. But unless nephritis already exist, the great advantages of the cold-bath method of treating typhoid fever outweigh any hypothetical harm to the kidneys. As a matter of fact, when liquids are allowed freely, as in typhoid fever, and when the baths are properly administered, the amount of urine is increased and the amount of solids and toxines eliminated is also increased. And while the kidney is called upon to do this increased amount of work, the lessening of toxæmia is one of the prime objects aimed at in the treatment of the infectious disease, and has a favorable influence in warding off nephritis. The favorable effect of the cold bath on the circulatory and nervous systems has indirectly

a favorable effect on the kidney. Senator is fully convinced that bathing, even cold bathing in fevers, including scarlet fever, is not productive of renal harm.

Drugs are sometimes used so freely as remedial agents as to induce nephritis. Alcohol may be given in too large amounts. Especial caution is necessary in the use of salicylic acid and its compounds, turpentine, copaiba, carbolic acid, corrosive sublimate, chlorate of potassium, and other remedies mentioned under the head of Etiology. Some of these may be harmful through absorption from the skin. Lüthje's[1] observations on albuminuria and cylindruria following the use of salicylic acid compounds are very instructive. When large doses of any of these drugs that are known to be irritants of the kidney are being given, the urine should be carefully watched, and albumin, casts or blood not interpreted in too offhand a manner as due to the infectious disease, and therefore an indication for still larger doses of the medicine employed, but as possibly directly connected with the injudicious drugging. It goes without saying that the prompt proper handling of a case of poisoning by such drugs as carbolic acid, chlorate of potassium, bichloride of mercury, etc., may prevent a serious acute nephritis.

Active Treatment.—There is no specific for acute nephritis, no matter what its cause. The cardinal principles underlying the active treatment are: (1) The removal, when possible, of the cause. (2) Rest for the kidney, secured by throwing less work upon it, and by calling upon other organs, *e. g.*, the skin and the bowels, to do vicariously some of the work of the injured organ. (3) To treat symptoms and complications as they may arise. If the cause is promptly remediable, as in malaria or syphilis, or when there has been alcoholic excess or too free use of irritating drugs, improvement may be prompt, but is still uncertain; the damage to the kidney has been done, and even the removal of the causal disease may not be followed by the prompt subsidence of the renal symptoms. Yet it is, of course, the proper thing to do in every case, to seek out the cause, and, if possible, remove it.

The patient should be kept in bed. He should be warmly covered and may with advantage sleep between flannel blankets or wear flannel or Canton flannel nightclothes. Fresh air in the sickroom is essential, but draughts should be avoided and the temperature of the room should be about 70° F. Strict adherence to the rule of rest in bed should be enforced until the disease has disappeared. In some of the more prolonged cases, however, bed life becomes very irksome, and some liberty in the way of sitting up or even of moving about may be permitted. This affords relief from the monotony of the recumbent posture, and while it may increase somewhat the amount of albumin in the urine, this drawback is fully compensated for by an awakening of interest on the part of the patient, an improvement in the appetite, better sleep, and better elimination.

An important question and a very live one in each individual case is that of diet. No hard and fast rule can be given applying to every case. The food should be such as will not, when its residual metabolic products are eliminated, throw too great a burden on the kidneys, by reason of amount or quality. The food, too, should be such as can be easily tolerated by the irritable stomach and bowels, so often met with in nephritis, and such that its digestion is simple and not attended by the formation of faulty by-products, whose

[1] *Deutsch. Arch. f. klin. Med.*, lxxiv, 163.

absorption may be a still further cause of damaging the diseased kidney. The food that most nearly meets the requirements is milk, and this may be given during the entire course of the disease, at first perhaps alone, later with other foods. It may be said that early in the disease it is often better to give the stomach absolute rest for a day or two, no food being allowed unless the patient craves water, of which a little may be taken. In many cases of the scarlatinal type, the onset, as already described, is more or less explosive, and among the symptoms are severe nausea and vomiting. Milk, often even water, given at such a time merely excites attacks of retching, and it is worse than useless to attempt to force the patient to take it. It is difficult to make some parents understand this point, as they feel that as the child is sick, he should at once be given medicine to check the disease, and plenty of food to keep up the strength. But a little explanation will usually enable them to see that the starvation for a day or two is really a kindness.

The question of the *amount of water* or other fluid to be allowed an acute nephritic has been quite actively discussed of late, especially since von Noorden has emphasized the fact that if the inflamed kidney is to have rest, and if one of its functions is the elimination of water, the amount ingested should be restricted. The flushing-out process advocated by those who prescribe huge amounts of water he regards as unsuccessful, for the damaged organ refuses to eliminate the increased amount of water and the flushing of the tubules is not accomplished, and as illogical, because it is asking an injured, inflamed part to do an increased amount of work, when what it needs is a temporary rest. There is much truth in this view. The water, if given too freely when the kidneys are refusing to secrete more than four or five ounces daily, goes largely to increase the œdema. At first, then, water and milk, or other liquid as well, may with propriety be restricted to a few ounces a day. The writer has found it a fairly good rule to be guided largely by the thirst of the patient. A thirsty patient, craving water, may be given one to two quarts of fluid a day, provided the stomach will tolerate it. The bowels, skin, and respiratory tract may be relied upon to take care of its elimination. The attempt to force a patient at this early stage to drink a gallon of water a day in addition to much milk is unwise; not only will the kidney be unable to handle this large amount, but there is some danger that the flooding of the vessels with an unusually large amount of water may unduly strain the heart.

Milk as an exclusive diet cannot with advantage be continued for too long a period; it becomes monotonous, and the amount required to maintain strength is something like three or four quarts daily, an amount that few individuals will tolerate for any great length of time. To the quart or quart and a half of milk may be added, therefore, cream, which is rich in calories; and cereals may also be taken, breakfast foods, oatmeal, sago, rice, farina, etc. Fruits are not injurious, baked apple, apple sauce, orange, lemonade, grape-fruit being relishes and acting perhaps as diuretics as well. A diet made up largely of fatty and carbohydrate foods leaves less residue in the shape of solids for elimination through the urine.[1] These foodstuffs, with but little of the proteids—possibly even less milk than is ordinarily prescribed—would seem to be peculiarly suited to cases of nephritis in which one wishes to

[1] K. Hanseen, *Nord. Med. Arc.*, 1906, Abt. ii, No. 10.

spare the kidney excessive work. Meat and broths should at first be forbidden. If the disease is prolonged, the craving for meat may become great and may with safety be satisfied by allowing a little meat once daily, such as a bit of bacon, chicken, fish, or even dark meat, like beefsteak, roast beef, or mutton. The prejudice against the red meats as opposed to the white has surely been largely unwarranted, and while it is unwise to allow a patient with acute nephritis large amounts of meat of any kind, later the taking of a small amount, even of dark meat, is permissible. Broths of various kinds and beef tea are better omitted until convalescence, as they are rich in extractives and may be injurious. Green vegetables, such as lettuce, celery, green peas, string beans, may be taken in small quantities after the acute stage has passed, when bread and butter, toast, crackers, zwieback are allowed.

The diet, then, at first should be milk; water is allowed in moderate amounts, thirst being a fair guide as to the amount, yet a total of more than two quarts of fluid daily being rarely exceeded. Later, in addition to the milk, cereals, fruits, gruels, green vegetables, and even some meat may be added. Rich and highly seasoned or spiced foods, fried and greasy foods, the sweets, such as cakes, pastries, pies, puddings, candy, etc., are best let alone. Salt should be reduced to a minimum, especially when œdema is marked. No alcoholic drink should be allowed.

Elimination should be favored in every way; the kidneys should be encouraged to act, and the skin and bowels should be made the vicarious agents for performing some of the work usually performed by the kidney. Nature apparently works in this way through these channels, and also through the respiratory tract. Practically, we can imitate nature to a slight degree only, in helping elimination through the respiratory tract. We may see that the patient is not deprived of his right to fresh air, which quite often, because of the overzealous efforts of attendants to prevent his "taking cold," is too rigorously shut out, and we may also by attention to the action of the heart and by not permitting pleural transudates to become too large, see that there remains no preventable hindrance to free respiratory action.

The bowels should be kept open. Saline laxatives are preferable when they are tolerated by the stomach. A dram to one-half ounce of Epsom or Rochelle salts or phosphate of soda, taken in one-half glass to one glass of water, the first thing in the morning, will usually secure free watery movements of the bowels, and may also lower blood pressure. Many of the natural or prepared saline laxative waters will answer equally well, *e. g.*, Hunyadi, Rubinat, Carlsbad, etc. In other instances the vegetable laxatives taken at bedtime seems to work better, *e. g.*, cascara, senna, or the pill of aloin, strychnine and belladonna. An occasional calomel purge is often very beneficial, and, especially when nausea is extreme, the use of calomel in often repeated small doses (gr. $\frac{1}{10}$ to gr. $\frac{1}{2}$) will move the bowels and at the same time act helpfully in allaying the nausea. Brisker and more promptly acting cathartics may be required, especially when acute uræmia seems impending, and under these circumstances elaterium (or elaterin gr. $\frac{1}{16}$ to gr. $\frac{1}{10}$), compound jalap powder, or even a drop or two of croton oil may be used. Elaterium too long continued irritates the stomach, and may be depressing. Enemas may prove of material help in keeping the bowels open, but in general in acute nephritis a little more thorough cleaning out of the alimentary tract is desired than that brought about by enemata, and some of the remedies just mentioned will by preference be employed, oftenest the salines.

All *diuretics* are liable to fail in acute Bright's disease, as the kidneys are in such condition that they will not respond to any influences. Milk and water are among the simplest and best diuretics. Lemonade is also excellent, and to this may be added cream of tartar, one teaspoonful to the pint of lemonade, the cream of tartar being first dissolved in hot water, as it is poorly soluble in the cold. The lemonade thus prepared is taken cold or hot, as the patient prefers. If taken freely, this is diuretic and laxative. With a weak heart and low blood pressure, digitalis and caffeine are of service in increasing the flow of urine. The citrate or acetate of potassium or sodium may be given in doses of from 10 to 30 grains (gm. 0.6 to 2) to an adult, and seem to be non-irritating. Excreted as carbonates, they tend to alkalinize the urine and also increase its flow. Sodium theobromine salicylate (diuretin), in doses of 60 to 90 grains (gm. 4 to 6) a day, is sometimes efficient, although its effects are often limited in acute nephritis, where the renal epithelium has undergone so great damage. Diuretin, like caffeine, is of especial value when the heart is weak. Cantharides, copaiba, cubebs, turpentine, that are sometimes advocated as diuretics, are far too irritating to the kidneys to be employed. Even gin, the household diuretic, is best avoided. And it is well not to push to the limit some of the simpler diuretics, such as the citrates and acetates, because of a possible harmful influence.

Due attention should be paid to the *skin*. Not only, as has already been stated, should it be kept warm, draughts and exposure to cold being avoided, but efforts should be made to secure free diaphoresis as a means of elimination. The amount of toxic material got rid of in this way may not be great, but there is some that escapes with the sweat. Patients, as a rule, express themselves as feeling better, and they have that appearance; and blood pressure may be lowered. Simple lukewarm or hot tub baths, or, if the patient is too weak, sponge baths, are of benefit. A sitz bath or a good soak in a tub of hot water, followed by a rubdown and immediate rest in a warm bed, is often the means of promoting free action of the skin and also of the kidneys. If quite hot water be employed, it is well to keep a cool cloth to the head during the bath. If thirsty, the patient may take a drink of water or of lemonade. The hot bath or the sweat in nephritis must be watched. Occasionally a patient does badly, becomes cyanotic, feels faint, and has a feeble pulse. Such patients must be given a shorter bath or a lukewarm one only, or this plan of treatment must be given up entirely.

Sweats are especially indicated when œdema is marked. Any procedure may be legitimately employed that will induce free action of the skin without inducing too great weakness and without exposing the patient to the subsequent influence of cold. The objection to pilocarpine (gr. $\frac{1}{12}$ to gr. $\frac{1}{6}$) is that it is a cardiac depressant. It will induce profuse diaphoresis. But an effect not desired is a profuse bronchial secretion; with the weakened heart too many of the phenomena of œdema of the lungs become manifest, either for the good of the patient or the mental comfort of the physician. Occasionally in patients who sweat poorly by the external application of heat a small dose of pilocarpine (gr. $\frac{1}{12}$) may be given hypodermically as an adjuvant. Large doses are certainly dangerous. It is to be remembered that pilocarpine once given differs from the ordinary means of inducing sweating, for its effects cannot be checked at will. With sweating by external means the further continuance of the diaphoretic measure can be promptly stopped if untoward effects are noticed—an advantage of no mean importance.

Various means for applying heat externally have been devised. A simple measure is to have the patient sit on a cane-seated chair, with a blanket pinned about his neck, thus making a tent covering the body below that point, and then to place a lighted alcohol or kerosene lamp beneath the chair. After a short time the body drips with sweat. Care must, of course, be exercised not to blister the patient and not by accident to set fire to the blanket or the patient's nightgown, if he wishes to wear one. The electric light sweat baths are an efficient means of securing the result, and the danger of accident by fire is avoided. When patients are too weak to sit up, some means for sweating them in bed must be employed.

A method easy of application is to make a tent of blankets or rubber sheeting over the patient, the blankets being held up by supports, such as half-barrel hoops. Into this tent a stovepipe of narrow caliber, such as any tinsmith can furnish, is conducted. This pipe, by an elbow, reaches nearly to the floor, and under its lower opening an alcohol or other light is placed. By this means the heated air is conducted into the tent in which the patient is lying, and a sweat is easily given. The method in vogue in the Presbyterian Hospital in Chicago serves admirably. The patient lies between blankets, and outside either blanket, the one under as well as the one above the patient, is a heavy rubber sheet. Hot bricks, in bags for convenience of handling, are placed about the patient, the blanket being so rolled that the body is protected from the brick by the cloth of the bag and by the thickness of the blanket. Alcohol is poured over the bricks and the blankets tucked in around the patient. A cold cloth is kept on the forehead during the sweat. A drink of lemonade is given before the sweat and during it, if the patient desires. In from twenty minutes to an hour, the length of time depending on the amount of sweat, the condition of the pulse, and the comfort of the patient, the procedure is stopped, the bricks are removed, the patient rubbed dry, and the damp blankets being taken away he is left on the warm dry sheet that had been previously arranged beneath the lower rubber blanket. Sweats of one kind or another may be given once or twice daily, or less often, depending on the degree of œdema and the effect on the patient.

Elimination, therefore, is secured, as far as possible, through the kidneys, by means of water, milk, and various non-irritating diuretics; through the bowels by laxatives, and through the skin by warm baths or by sweats.

Complications and annoying symptoms must be treated as they arise. Some of these will be discussed more fully in treating of chronic nephritis. The œdema may demand not only the sweats, but puncture of the legs, paracentesis of the abdomen or of the pleura. Œdema of the larynx occasionally necessitates scarification or even tracheotomy.

Drugs supposed to act as specifics in acute nephritis are of no benefit whatever, and it is useless or even harmful to give large doses of tannin, ergot, or methylene blue in the hope of effecting a cure. Surgery (acupuncture, splitting the kidney, decapsulation, etc.) has a very limited field in the treatment. This will be taken up later.

Pain over the kidney is often relieved by the hot-water bag, the electric pad (heat), or by a mustard paste. Blistering is unnecessary. At times vigorous counterirritation seems to relieve not only the lumbar pain, but an increased flow of urine is excited; the congestion of the kidney seems to be somewhat lessened. Severe headache occasionally requires bromide or even morphine. The latter drug, theoretically locking up secretions, should in

general be used sparingly in acute Bright's disease, but in some instances the effect is to increase the output of urine rather than to diminish it.

After the acuter stage much good may come from the use of some of the bitter tonics. Appetite and digestion may be much improved by nux vomica and hydrochloric acid. When anæmia is marked, and especially when convalescence is delayed, iron is of great value. Some of the scale preparations of iron may be employed, or Blaud's mass, or even the tincture of the chloride of iron, although this preparation is not always well tolerated by the stomach. It is here that Basham's mixture (mistura ferri et ammonii acetatis) may serve a useful purpose. When freshly and carefully prepared by the pharmacist, it is not only a clear, transparent, reddish-brown solution, but it is not unpleasant to take, is non-irritating, and in doses of ʒj to ʒiv (4 to 15 cc.) often acts not only as a hæmatinic but as a diuretic.

Cardiac stimulation may be necessary. Strychnine is here of service, and digitalis especially when blood pressure begins to fail. This remedy as well as strophanthus and caffeine have also the effect of increasing the flow of urine, as they improve the strength of the heart's beat and raise blood pressure.

Practically nothing has been accomplished in the way of treating acute nephritis by specific bacterial products. Yet if microbic etiological factors can be definitely identified as the cause of a given case of nephritis there may be promise in the use of specific sera or of the so-called vaccines that have been used quite freely since Wright's work on opsonins. Some measure of success will, it is to be hoped, attend the attempt in such cases to remove the operating microbic cause, as is done now when it is the diphtheria germ. Microbic pyelitis may be treated with specific serum or vaccine—and work of this kind has been done in this condition—and consecutive nephritis be prevented or ameliorated. The possible damaging effects of specific sera and vaccines on the kidney are matters for careful consideration.

CHAPTER VII.

CHRONIC PARENCHYMATOUS NEPHRITIS.

By JAMES B. HERRICK, M.D.

Chronic parenchymatous nephritis is in many respects similar to the acute form; not a few cases of the chronic type are known to develop from acute nephritis. Occasionally the parenchymatous form seems to run by imperceptible stages into the so-called secondary contracted kidney. These facts have been used by those who argue for the unity of all forms of nephritis, to prove that these are in reality not different types of the disease, but merely three stages. But, as has already been said under the subject of classification, a form of nephritis with fairly definite symptoms and clinical findings and with a fairly uniform anatomical lesion in the kidney may be recognized, to which the name chronic parenchymatous nephritis may well be applied. It must, however, be freely admitted that the term, in a sense, is a misnomer, as the pathological process is *always diffuse*, and that the type, as already stated, shades imperceptibly on the one hand, into the acute form, and on the other, into chronic nephritis with induration and contraction. The description of this form of disease may be made rather brief, as in many respects the description already given of acute nephritis will apply as well to the chronic parenchymatous form.

Etiology.—In most cases no definite cause can be assigned. Some factors, however, that when operating suddenly or with great intensity produce acute nephritis, may, if operating for a longer period or less severely, produce the chronic form of the disease. Thus, long-continued exposure to *cold* explains its not infrequent occurrence in those who live or work in damp cellars, also in bakers, butchers, and icemen. *Alcoholism* may also produce it. The acute *infectious diseases*, such as scarlet fever and malaria, which oftener produce the acute form, are said by many to produce the chronic form at times, or the acute form passes over into the chronic type. Malaria has been regarded by many—Rosenstein, Bartels, Thayer, and others—as a frequent cause of this type of nephritis. On the other hand, Wagner and some other writers dispute this fact. While direct proof that the *gonococcus* is the cause of acute or chronic parenchymatous nephritis is not easily available, the writer believes that it may occasionally produce such an inflammation. The more we learn of the gonococcus the more does it appear as a frequent systemic invader. Lurking in the prostate, the joints, or the Fallopian tubes, it may, long after the acute manifestations have disappeared, give rise to acute or chronic inflammatory inflammations in various organs or tissues, and among these may perhaps be, oftener than we think, the kidney. *Chronic intoxications*, where one must assume the condition of altered blood, may produce irritation and ultimately inflammation of the kidneys. Thus, it is seen occasionally in lead or mercurial poisoning; also in connection with syphilis, diabetes, or suppurating disease.

Mention must be made of the frequent occurrence of chronic parenchymatous nephritis in connection with *tuberculosis*. This fact is emphasized by most writers, and some go so far as to state that 25 per cent. of the cases of chronic parenchymatous nephritis are in association with tuberculosis. One must remember here, however, the difficulty of distinguishing between the acute and chronic forms of the disease, some of the cases probably being acute; and, again, we must remember the not infrequent occurrence of amyloid disease with tuberculosis. Unquestionably, some of the cases reported as chronic parenchymatous nephritis have been but instances of amyloid disease; in others these two conditions have been associated. But, making allowance for the cases of acute nephritis and of amyloid disease that have been wrongly classed as chronic parenchymatous nephritis, the fact remains that pulmonary tuberculosis is the most frequent cause of chronic parenchymatous nephritis. Occasionally, in connection with valvular heart disease, the condition of *cyanotic induration* or chronic passive congestion seems to give rise to this form of Bright's disease; though, as Rosenstein and Senator have suggested, there is a possibility that the heart disease and the kidney disease are due to one and the same cause, rather than that the lesion in the kidney is entirely secondary to the cardiac condition.

Mention may be made here of the views of Semmola, who fifty years ago announced the belief that albuminuria was not due to a lesion in the kidney, but was rather the cause of such lesion. Some primary alteration of the blood, making *albumin* more diffusible, or rendering it *non-assimilable*, permitted it to leak through the kidney and in this way irritate and inflame this organ. While these views of Semmola have not had general acceptance, there is still some reason to believe that in many cases the primary change is in the character of the albumin in the blood, rendering it non-usable and, therefore, on the order of effete material that is to be eliminated, and that in the process of elimination the inflammation of the kidney is produced.

Pathological Anatomy.—There is no one form of kidney that is uniformly found in cases regarded during life as chronic parenchymatous nephritis. Just as clinically the disease seems to shade off gradually, on the one hand, into the acute nephritis, and, on the other, into the chronic interstitial, so anatomically the kidney often bears close resemblance to these other forms of nephritis. It is to be particularly borne in mind, as already stated, that the process is always diffuse and never limited solely to the parenchyma proper. It is largely owing to these varying degrees to which the interstitial fibroid process is present that several varieties of chronic parenchymatous nephritis have been described.

What may, perhaps, be regarded as the type is the *large white kidney* of Wilks. While in its classic form not so very commonly seen, it is nevertheless not rare, and approaches most closely the kidney in which the inflammatory and degenerative process is definitely chronic and preëminently affects the renal epithelium. This kidney is enlarged, weighing about 250 to 300 grams (Fagge mentions a pair of kidneys weighing 29 ounces), and light gray—even almost white—in color, the stellate veins showing distinctly. The kidney is soft, and on section the thin capsule is found to strip readily, leaving a non-granular surface. The cortex is swollen and pale yellow or grayish. It may be as wide as the medulla instead of one-third the width. The dark pyramids with their streaked markings show in striking contrast to the light and more homogeneous appearing cortex. The cortical markings

are usually indistinct, and dull opaque spots or streaks are often to be made out in the midst of the more translucent areas. Minute reddish dots may be occasionally seen, due to hemorrhages (chronic hemorrhagic nephritis).

Microscopically, there is a marked degenerative change in the *epithelium* lining the tubes, especially marked in the convoluted tubules. Individual cells are swollen, granular, fatty, with outlines often indistinct. The nuclei may be fragmented or invisible. Often the cell has slipped from its place into the lumen of the tubule, where it is seen as a fragment with ragged edges, or represented only by granular detritus or fat droplets. The swollen cells may narrow the lumen of the tube, or by their desquamation the caliber may be increased. Casts of different kinds, epithelial cells in various stages of degeneration, granular debris, fat globules, and red and white blood corpuscles, may crowd the tubule.

The *Malpighian bodies* show varying changes, much as in acute nephritis. They are usually enlarged. Epithelium with fatty degeneration is often seen in the glomerulus proper and in the capsule. Proliferative change with nuclear multiplication is frequently one of the striking lesions. Swollen, desquamated, and degenerate cells may fill the capsular space, and the capsule may be denuded or exhibit a lining of freshly proliferated cells. Red and white corpuscles may crowd the space (hemorrhagic form), or it may be distended with a clear inflammatory exudate, pushing the capillary tuft to one side. The wall of the capsule may be thickened, and in some instances show slight fibrous growth. The capillaries may show hyaline changes in their walls and are often thrombosed.

The intertubular *connective tissue* shows varying degrees of œdema. Round-cell infiltration may be here and there present. Small hemorrhages may have occurred; in these cases pigment granules may be seen in the connective tissue (Ziegler).

Many variations from this type of the large white kidney have been described, being dependent partly on the color, consistency, and size, and partly on the degree of fibroid change present. The predominance of fatty changes produces the white or grayish color. If this kidney at the same time has somewhat advanced interstitial changes with contraction, it is smaller, firmer, and with capsule thickened and adherent in places, and the surface rough and granular. Bowman's capsule will show thickening and the glomerulus itself may be atrophied or its place taken by fibrous tissue. This is the small white kidney, a combination apparently of the fatty degenerative process, with marked induration as well, the latter at times a sequel of the earlier parenchymatous change—*secondary contracted kidney*—though in some instances these processes are perhaps coincident. Some of these kidneys are above the normal in size, and are, therefore, in the strict sense not contracted.

In all these forms the kidneys are not uniformly affected, markedly involved areas often appearing in the midst of seemingly healthy tissue. In some instances this patchy distribution is seen even with the naked eye. Some describe as a separate variety of chronic parenchymatous nephritis a kidney of large size, mottled with reddish and light areas—representing respectively small hemorrhages or highly vascular areas, and fattily degenerated and relatively anæmic tissue—with slightly adherent capsule, the organ being firm from abundance of connective tissue. This is the large red kidney, or *variegated kidney*.

The microscopic fatty degenerations are the same as in the large white kidney, though generally less in degree. Minute hemorrhages are more numerous and fibroid changes more marked.

Symptoms.—The striking features in the clinical manifestations of chronic parenchymatous nephritis are the slow, insidious onset, the characteristic urinary findings, and the marked degree of œdema. Cardiovascular changes vary very much, as do the uræmic manifestations. In most instances the physician is consulted either because of vague, indefinite symptoms, such as malaise, poor appetite, disturbance of the stomach or bowel, general weakness, or because some puffiness has been noted about the eyes or about the ankles. When an examination is made, one of the most striking changes is found in the urine.

The Urine.—The amount is diminished. On an average, perhaps 500 cc. would be the daily output of a patient with this form of disease. The specific gravity in general is normal or slightly above normal. The urine is acid. It is dark in color and often turbid. Occasionally there is a distinct opalescence from the presence of numerous fat globules. On standing there is an abundant sediment that under the microscope is found to consist largely of urates, casts, white and red blood corpuscles, epithelial cells, and amorphous debris. The reaction for albumin is prompt and shows a large amount. This is particularly true of the day urine. The quantity is ordinarily from 0.5 to 2 per cent. When the estimate is made by bulk the albumin will be found to be from 25 to 75 per cent. The total amount lost during the day will run anywhere from 5 to 30 grams. Exceptionally, larger amounts than this have been noted; some record as high as 5 and 6 per cent. of albumin. The urea and solids are diminished absolutely. Relatively, however, they are usually in normal or even increased amount. Sometimes they are so deficient that the specific gravity of the urine is lowered, even though the total amount is decidedly lessened. In case improvement occurs, or there is the development of the secondary contracted kidney, the amount of urine will increase sometimes to as much as 5 or 6 liters. The specific gravity will be greatly lowered and the percentage of albumin will be decidedly lessened. The absolute amount of solids will be increased. The freezing point of the urine in this form of nephritis is sometimes lower than normal, although it is influenced much by the degree of œdema and anæmia, the blood pressure, etc. Rarely it will be found as low as —2.6° C., oftener in the neighborhood of —1° C. As an aid in the diagnosis of chronic parenchymatous nephritis cryoscopy is of little value. Some slight value might attach to it from the standpoint of prognosis when combined with cryoscopy of the blood. This whole subject is discussed more fully elsewhere.

From time to time there are variations in the amount of urine, depending largely upon the condition of the heart, the blood pressure, the amount of food and drink, the degree of œdema, and the condition of the bowels. The microscopic study of the urine shows casts of nearly every variety. Hyaline and granular casts are abundant, and many of the latter are dark in color and contain coarse granules. Numerous broad casts are also seen. Waxy casts and casts with oil globules upon them are very common. Renal epithelial cells, many of them showing marked degenerative changes and covered with fat globules, are found in abundance. Occasionally cases are reported in which casts are said to be absent, even though the amount of albumin is abundant. This may exceptionally be true, but the explanation is perhaps

to be found in faulty technique, or in the fact that the urine presented for examination is old or has undergone decomposition in the bladder. That casts may be dissolved by the presence in the urine of some pepsin-like body, has been shown by Sehrwald. Wherever such an anomaly, therefore, seems to be present, great care should be exercised in noting the reaction of the urine and in trying to secure a specimen that is perfectly fresh.

Œdema.—The œdema in this form of Bright's disease usually begins rather slowly, and is first noticed as puffiness of the eyelids in the morning or about the ankles at night. It gradually increases, however, until we find the patient in the marked cases presenting an extreme degree of anasarca, with the face swollen, and the wrinkles that give expression to the countenance obliterated, the hands, the arms, the back, the legs, all showing marked œdema. One of the most annoying and one of the most striking complications is the œdema of the loose tissue of the penis and scrotum. This may be extreme, and even cause some difficulty in urinating. The serous cavities often contain fluid, and ascites and hydrothorax may be extreme and interfere seriously with the function of the abdominal and thoracic organs, as already referred to under the head of "acute nephritis." Rarely, there is a localized œdema, and one sees the collection of fluid limited to one pleural cavity, to the scrotum, or to the legs. Usually, however, it is decidedly general. Together with the œdema there is more or less anæmia. This is due to the fact that the red blood corpuscles and hæmoglobin are actually diminished, and also to the fact that the blood is thinned because of the condition of hydræmia. The capillaries also are spread out over a more extensive surface, so that the anæmia is apparently greater than it really is. With the œdema the anæmia gives to the patient a peculiar puffy, pasty-like appearance which is quite characteristic, and enables one sometimes to make a diagnosis almost at a glance. The œdema, when extreme, causes a marked increase in the weight of the patient, and he is sometimes greatly deceived in thinking he is gaining in weight and, therefore, improving, when, in fact, he is merely accumulating more and more water in the tissues. When, perhaps, the œdema disappears rather suddenly, the patient is seen to be greatly emaciated, and the skin hangs in loose folds, where before it had been tense with the accumulated fluid.

The dangers from the œdema have already been referred to, but it may be well to call attention again to the fact that the waterlogged condition of the wall of the stomach and of the bowel interferes seriously with the performance of function of these two organs. The pressure of the fluid in the pleura and pericardium, as well as the upward pressure of the fluid on the diaphragm, when ascites is marked, interferes very much with the action of the heart and of the lungs. The patients are frequently obliged to sit up at night in order to breathe. The swollen condition of the legs and thighs, together with the general weakness, makes it impossible for some of them to move about with any degree of comfort, so that their life really consists in lying in bed or sitting up in a chair. The tense skin may rupture or become abraded, and then, if infection occurs, annoying or even serious inflammation may be the result.

Reference has been made to the gastro-intestinal disturbance that comes from œdema. While œdema does not explain all of the disturbance, there is no nephritis in which the digestion is more interfered with than in this form. The appetite is often poor, and patients have a loathing for ordinary

simple food. There is nausea, not infrequently vomiting; a feeling of fulness and weight amounting to positive distress or pain is sometimes complained of after eating. The bowels may be constipated, but are often loose; ulceration of the intestine is occasionally an explanation for this diarrhœa. The tongue is coated; there is a fœtid odor to the breath. This poor digestion is one reason for the great loss of strength, for the anæmia, and for the emaciation from which these patients suffer.

Changes in the *heart and bloodvessels* are commonly present, although they are by no means so marked as in the cases of chronic interstitial nephritis. They may be entirely absent. In a patient now under observation, in whom albumin has been abundant in the urine for two years, œdema is pronounced, and other symptoms indicate chronic parenchymatous nephritis, there is no evidence upon physical examination of increase in the size of the heart, no ringing aortic tone, and the blood pressure is only 113 mm. Hg. If secondary contraction occurs, then cardiovascular changes become pronounced. Senator believes that in chronic parenchymatous nephritis the hypertrophy of the heart, which is often met with, is eccentric, that is, with dilatation as well as hypertrophy. The dyspnœa of which these patients complain is often cardiac in origin from this dilatation. Myocardial degeneration will also aid in explaining the dyspnœa, although the anæmia, œdema, and uræmia as well may contribute to produce the shortness of breath.

Uræmia is generally present, and while not such a striking feature as in some cases of acute nephritis, or in the typical chronic interstitial nephritis, still offers the explanation of many of the symptoms complained of by these patients. The malaise, some of the gastro-intestinal disturbances, such as vomiting, headache, sleeplessness, are in many instances undoubtedly uræmic in character, and as the disease goes on some patients have definite uræmic manifestations in the shape of almost unbearable headache, convulsions, or coma. Retinitis and optic neuritis may occasionally be seen. Rarely, the amaurosis not infrequently met with in the contracted kidney is seen in this form of Bright's disease.

In some cases, after the evidences of chronic parenchymatous nephritis have lasted for many months, a change occurs which is quite remarkable, the dropsy becoming less, and finally entirely disappearing, the urine increasing in amount, becoming lighter in color, lower in specific gravity, and containing a smaller number of casts and a smaller percentage of albumin. The condition of *secondary contracted kidney* has now appeared, and while the patient may flatter himself that he is decidedly better, or even entirely well, the careful physician will find on examination that the urine is always albuminous, always contains a few casts, and will note particularly that hypertrophy of the left ventricle is developing, with all the evidences of increase in blood pressure. Later the cardiovascular changes become still more pronounced. The manifestations of uræmia appear, and the case runs the course of an ordinary contracted kidney. Through this somewhat favorable termination of chronic parenchymatous nephritis life may be prolonged for many months, sometimes for several years.

Complications.—The complications referred to under the head of acute nephritis are practically those that are met with in chronic parenchymatous nephritis. Pneumonia, bronchitis, or œdema of the lungs may become serious and even the cause of death. Inflammation of the serous membranes —pleuritis, pericarditis, peritonitis—is met with. Intercurrent infections,

like erysipelas, may occur. Death is brought about at times from dilatation of the heart or from myocardial weakness. Alimentary disturbances in the shape of acute gastritis or enterocolitis may be extreme and sufficiently pronounced to be looked upon as serious complications.

Diagnosis.—There is no difficulty whatever in diagnosing the existence of nephritis in cases of the type under discussion, provided the urine is examined. An abundance of albumin and casts leaves no question whatever as to the existence of nephritis. The marked œdema also helps in making this diagnosis. The only question that arises is as to the variety.

From *acute nephritis* differentiation is oftentimes impossible unless one knows the early history. A knowledge of the existence of the causal factor, as, for instance, some acute infectious disease, the sudden onset with hæmaturia and relative anuria, makes the diagnosis comparatively easy. An abundance of red blood corpuscles in the urine speaks for acute nephritis. Yet it must be remembered that in the chronic form microscopic blood may be found and occasionally a hemorrhagic type is seen with frequent renal hemorrhages causing hæmaturia of such severity as to be noted by the naked eye. In many cases, however, an attempt to differentiate between the two is unavailing, and one must be satisfied in saying that one is dealing with parenchymatous nephritis without trying to tell whether it is acute, subacute, or chronic, and without making a vain effort to draw an artificial line between them.

From *chronic interstitial nephritis* of the typical variety the differentiation is easy. The abundance of albumin and casts, the marked œdema, the slight degree of cardiovascular changes, are all in such striking contrast to the marked cardiovascular changes, the absence of œdema, the large amount of urine of low specific gravity and small amount of albumin and casts that are met with in contracted kidney, that the differentiation is simple. When the *secondary contracted* kidney exists, differentiation from the primary contracted kidney is made by the preceding history of œdema and marked albuminuria. Yet many of our efforts to fit these cases of nephritis into definite pigeon holes and label them as chronic parenchymatous or chronic interstitial nephritis are really useless because, as has been said, the cases often from the beginning are of a more diffuse character and present the characteristics of both types of disease. The best diagnosis that can be made here is chronic nephritis, or simply *chronic diffuse nephritis*. Cases of this character usually show some cardiovascular change and have uræmic symptoms, perhaps retinitis, like the chronic interstitial variety; but they show the œdema of renal origin, a urine rich in albumin and casts, and often of a specific gravity that is about normal or perhaps just a little below normal, *i. e.*, some characteristics of the chronic parenchymatous type. To a case of this kind the name chronic nephritis, without any qualifying adjective, had best be applied, or one may employ Müller's expression and speak merely of a chronic disease of the kidney with dropsy.

From *amyloid* kidney the differentiation is not always easy, and is sometimes impossible because the two diseases may be combined. Amyloid may be suspected, however, when any cause for amyloid, such as syphilis, tuberculosis, or chronic suppuration, exists, and when, along with the urinary findings, an enlargement of the spleen and liver can be made out. In amyloid, too, cachexia is more pronounced and there is generally less universal dropsy. The urine may show great variations in amount, and casts are apt to be

fewer than in the chronic nephritis. Serum globulin is present in increased proportion. Uræmia and retinitis are relatively rare.

From *congestion of the kidney* the differentiation is usually easy, the œdema being in the lower part of the body, and there being a definite cause for the congestion, such as a weak heart. The amount of albumin is usually less than in the true nephritis; the casts are fewer, and the therapeutic test—giving the patient rest and cardiac stimulants, with resulting improvement in the condition of the urine—will usually clear up the diagnosis.

Prognosis.—This form of disease was once looked upon as entirely hopeless. Even now the prognosis is justly regarded as extremely bad. Yet patients corresponding in every respect clinically to chronic parenchymatous nephritis have been known to recover. The collective report of Cabot, made a few years ago, showed that many physicians of good repute had seen stray cases of recovery from chronic parenchymatous nephritis. The question always arises in these instances as to where to draw the line between acute nephritis, which admittedly often gets well, and the genuine chronic parenchymatous form of the disease. Dropsy has been looked upon as having an important bearing on prognosis, but there seems to be no rule as to this, and the case that is accompanied by severe dropsy may have as good a prognosis as the one in which it is not so very marked. Death, as a rule, occurs in from six to eighteen months. Some of the supposed recoveries, if carefully looked into, will be found to be instances in which the secondary contracted kidney has developed. Death occurs from exhaustion in the greatest number of cases, this exhaustion being brought about by inability to take, digest, and assimilate food, by the anæmia, and by the consequences of œdema. Death may also be brought about directly through the weakness of the heart, through some uræmic manifestations, such as convulsions or coma, or through some of the numerous complications already mentioned.

Treatment.—In the way of *prophylaxis* little can be done in any individual case, although the chronic alcoholic may be cautioned against the possible effects of his bad habits, and the worker in cold, damp places may be advised of the dangers of exposure to extremes of heat and cold; but in practice very little can be done in the way of prophylaxis.

In general, the *active* treatment is the same as in the acute form of the disease. *Rest* is of great importance. Rest in bed is usually instituted at the beginning of treatment, and the result commonly is that the albumin diminishes and the patient is for the time being better. Rest here should not be too absolute, however, and not be continued for too long a time. It becomes extremely irksome and monotonous, and when the disease is going to last for many months, one cannot expect a patient to stay in bed during all this period. It is much better, at times, to let the patient sit up and even indulge in a little exercise about the house, or in pleasant weather go outdoors. While the œdema may increase a little, and while the amount of albumin may also be increased, there is many times a distinct gain in the appetite and digestive power; the patient sleeps better and the anæmia is improved. Still the rule holds true that relative rest at least should be insisted upon in the early treatment of this form of nephritis. The patient should be warmly clad, whether in or out of bed, in order to avoid danger of exposure to cold. Woollen garments should be worn next to the skin.

The question of *diet* is an important one, and what has been said regarding acute nephritis will apply to chronic nephritis, yet the same restrictions

cannot be enjoined for so long a period. We cannot, in other words, keep the patient for months upon an exclusively milk diet. If we do, we find that the appetite disappears; nausea and diarrhœa are apt to occur, and there is great loss of strength and deterioration of the blood. Milk can, however, be one of the main articles of diet, and a patient may take with profit say a quart of milk daily, but in addition there should be other foods. Meat may be allowed in small amounts, perhaps once a day. It makes little difference whether the meat be light or dark. Cereals, such as oatmeal and the ordinary breakfast foods, rice, sago, farina, tapioca, may be allowed freely. Fruits are also in order. Lemonade is a good diuretic, and is frequently enjoyed by these patients. Some of the simpler vegetables may be taken. Broths should not be rich, nor should they contain too much meat juice. Gruels made up with water or with milk are not harmful. Fried and greasy foods; sweets, such as cakes, pastries, pies, candies, and desserts; all rich and highly seasoned foods, should be omitted or taken in very small amounts. Enough food should be taken to keep up the strength, and yet the physician should be cautious in not allowing the patient to overeat. There is seldom any danger of this because the appetite is usually so poor that the endeavor is rather to get the patient to eat enough than to prevent him from taking too much.

Water should not be taken in excessive amounts; it is not eliminated freely through the kidney, and tends to increase the œdema. When one considers the oliguria with accompanying or resulting renal insufficiency, and realizes that a plugging of the glomeruli, the capsular space and tubules, with exudate, debris, and casts contributes to produce this deficient elimination through the kidney, one feels like advising large amounts of water for the purpose of flushing out these channels. But whether or not water be regarded, in part at least, as a metabolic product, the fact is that the diseased kidney has lost its power of passing large amounts of water rapidly from the body, it has lost its "diluting power" (Koranyi), or elimination is, at least, delayed (bradyuria), so that an increase in the intake of water results not in polyuria, but in an increase in œdema. When, however, œdema is disappearing and polyuria has set in, one may assume more nearly patent glomerular vessels and tubules and a restoration of renal function in the way of power of eliminating water, and the amount of water ingested may now be increased and will be followed by a corresponding increase in the amount of urine and, one always hopes, by a still further removal, by washing out, of the material that has been obstructing the urinary channels. The rule is a fairly good one to let the patient take such water, milk, and other fluids as his thirst indicates. One and one-half to two quarts of fluid a day will represent a fair allowance. Wines, beer, and the stronger alcoholic drinks should not be allowed unless it be in exceptional cases, where a little wine may be allowed at meal times. Smoking is not necessarily to be prohibited. The morning cup of coffee is something that patients usually like to cling to, and, as a rule, there is no harm in allowing this.

Sodium chloride is frequently eliminated poorly by the inflamed kidney. Whether sodium chloride retention is a potent cause of œdema or whether both are merely phenomena of nephritis, with no relation of cause and effect, is a subject needing still further experimental and bedside investigation. Yet so many suggestive facts have been noted, the rapid fall of sodium chloride in the urine when ascites suddenly develops, its increase in the

urine when œdema is disappearing, the production at will of a rise and fall of the œdema by increasing or lessening the amount fed—and retained—to patients who have been experimentally observed, that one feels that there are many things that go to show a disturbance of water balance and alterations in osmotic pressure from chloride retention, that might easily result in an increase of fluid in the intercellular tissues.

Salt, therefore, should be reduced to a minimum. The amount of salt necessary in the body is usually supplied by that found in the bread and milk ordinarily ingested. While one cannot make any extravagant claims for the treatment of the œdema of nephritis by the withdrawal of salt—dechloridation—still the investigations of Widal, Javal, Strauss, and many others seem to indicate that in some cases, at least, an ordinary or excessive amount of salt in the food increases the œdema and albuminuria, while a reduction of the amount tends to lessen the same. It is wise, therefore, to limit the amount of salt ingested.

A point that is often not insisted on enough is that a patient with nephritis should be allowed the benefits that come not only from good food, but from fresh air. The fear of taking cold oftentimes leads the patient to shut himself indoors and to deny himself the privilege of fresh air. A change of *climate* will sometimes benefit these patients. Going to a warm, dry climate, the patient gets outdoors, and in that way he is greatly helped.

The *anæmia* of this form of nephritis is combated not only by the fresh air and the food but usually by the giving of iron. Some contend that very large doses of iron should be given—30 to 40 drops of the tincture of chloride of iron after meals. Iron is of great benefit in these cases, but the writer believes that James Tyson is right when he says that "large doses of iron should not be given. They are useless; lock up the secretions, cause headache, and increase the danger of uræmia." The writer gives *Basham's mixture* oftener than any other preparation of iron. This is easily tolerated by the stomach, is not at all unpleasant to take, and seems to have some diuretic action as well as to act favorably in improving the anæmia. The preparation, as obtained from the drug store, should be carefully looked after to see that it is not old, and the druggist should be instructed also to be particularly careful to make the mixture elegant and not permit it to get into the hands of the patient with muddy sediment, as sometimes occurs when the preparation has been hastily made and when not enough acetic acid has been added. The dose should be from 2 to 4 drams, three or four times a day.

Elimination in this form of nephritis is secured, as in other conditions, largely by the use of *laxatives.* Almost any laxative may be given, but the salines seem to act the best. The saline cathartics may be given on an empty stomach early in the morning, and enough should be taken to induce two or three rather loose watery stools. At times good follows from giving the salines several times during the day, or from using some of the stronger cathartics, like elaterin. This vigorous purging is apt to be rather depressing, and it is not always wise to secure a slight reduction in the œdema at the expense of the strength of the patient. Some of the vegetable laxatives, like cascara or senna, are also of value. Occasionally a dose of calomel will work beneficially.

The reduction of the œdema by means of *sweats* has already been referred

to under the head of Acute Nephritis. It is of interest to note that Bendix[1] finds in cases with the molecular concentration of the blood increased and the freezing point lowered, there is a tendency for the lessening of the molecular concentration and an approach toward normal of the freezing point by the use of sweats. When this is normal, however, no change is brought about by sweating. Fear has been expressed by some lest by sweating a too great concentration of toxins in the blood might result. Leube, for one, advises that liberal amounts of water be taken at the time a sweat is given, so that this tendency may be counteracted. Sweats may be given in any way that is most feasible. Many patients will get into the tub and take a hot bath of a temperature of 103° to 105° F., and then roll up in warm blankets in bed and sweat profusely. This is a very simple method. The sweat may be induced by the hot pack. The patient is rolled up in bed in a sheet wrung out of hot water, covered with blankets, and allowed to lie there for an hour or two, until he sweats profusely. The bath, by means of the hot bricks, as described under the head of Acute Nephritis, is a simple method and one that is especially suitable for hospital use. The electric light bath, or even the Turkish bath, where there are proper establishments, and where care can be given to the patient afterward to insure a prolonged period of rest and to see that he does not go out into the open air too soon, are methods of inducing sweat that are very efficient. Some patients undoubtedly derive great benefit from the sweat given once or even twice a day. Some become more or less cyanotic, the pulse becomes weak, and there is a feeling of great prostration following. The physician must judge in each case as to how long the sweat should continue as well as how often it should be given.

Œdema oftentimes calls for *aspiration* of the pleural or abdominal cavity, or puncture of the skin. When there is double hydrothorax of any considerable extent, and when dyspnœa is pronounced, aspiration should not be long delayed. With double hydrothorax sudden death has been met with more than once. While the fluid may reappear, still the drawing off of one quart or one quart and a half from the pleural cavity relieves the pressure upon the lungs, vessels, and the heart, and absorption is sometimes quite rapid after the aspiration. So, too, tapping of the abdomen is oftentimes followed by great relief in every way. The popular notion that prevails in Bright's disease, as well as in cirrhosis of the liver, that a patient who is once tapped will have to be tapped repeatedly, and will never recover, is, of course, without any foundation in fact. All of these operations should be done with strict asepsis, as there is considerable danger of infection of the skin, or even of the pleura or peritoneum.

The question of *draining the legs*, when the œdema is extreme, is one that arises very often, and the physician hesitates to make a puncture through the skin of the leg, knowing that the wound will remain open for many days and that there is great danger of infection. When a patient can have the services of a trained nurse, and when asepsis can be rigidly carried out, these punctures may be made with much more freedom than under other circumstances. The good results are sometimes very striking. Fluid oozes for many days, and the œdema of the lower extremities disappears as well as the œdema of the scrotum, and to a certain extent the ascites and œdema of the abdominal wall. The operation may be done in one of three ways. The writer

[1] *Deutsch. med. Woch.*, 1904, No. 7.

prefers many small punctures through the skin, made with the ordinary scalpel. Some prefer to make one large cut two or three inches in length down to the bone over the shin; while others prefer the use of the Southey tubes. Anyone of these methods is successful, and the dangers from one are about as great as from the other.

Attention should be paid to the condition of the *heart*, and the use of strychnine, digitalis, or strophanthus is sometimes clearly indicated. The good effects of digitalis are oftentimes seen in the increased elimination of urine as well as in the improvement in dyspnœa. Sleep is frequently disturbed in nephritis and may necessitate the use of bromides, or some of the *hypnotics*, like veronal or sulphonal. Morphine, or some other derivative of opium, in small doses is occasionally the best hypnotic to give. One must be very careful in using this not to give too large doses, and should also be careful not to induce the morphine habit. But there are many patients for whom a hypodermic of morphine given at night is the very best hypnotic to employ. Pain is rarely so great as to demand opiates. Sometimes the headache is extremely severe, and here opium will be called for. The treatment of the uræmic complications, such as coma and convulsions, is the usual treatment referred to elsewhere.

CHAPTER VIII.

CHRONIC INTERSTITIAL NEPHRITIS.

By JAMES B. HERRICK, M.D.

Introduction.—As already stated, three divisions of this form may be made: (1) Primary chronic interstitial nephritis; (2) secondary chronic interstitial nephritis; (3) arteriosclerotic kidney.

The secondary contracted kidney is a sequel of the chronic parenchymatous form; the arteriosclerotic kidney is but one manifestation of a general arteriosclerosis. The primary chronic interstitial nephritis, the "genuine contracted kidney," is the form that develops with no preceding acute or chronic parenchymatous inflammation, and in which the disease of the kidney is not simply part and parcel of a general arteriosclerosis, but is the primary underlying lesion, the cause oftentimes of a secondary general arteriosclerosis, but not a consequence of the same. In truth, however, it is no easy thing to classify these cases as they come to the physician, or even as the kidneys are studied in the dead-house. Secondary contracted kidney may closely resemble the primary form, and only a knowledge of the previous clinical history may enable one to recognize the true character. The relation of the renal lesion to the arteriosclerosis found during life and postmortem may be difficult to unravel. Three explanations are possible: (1) General arteriosclerosis may be primary, the kidney being secondarily involved. (2) The arteriosclerosis may be a result of primary renal disease that leads to cardiac hypertrophy and high blood pressure, *i. e.*, there is primary nephritis with secondary arteriosclerosis. (3) Or the vascular and renal conditions may be due to one and the same cause, developing independently of each other yet simultaneously. It may be added that some—and with much reason—object to the use of the term nephritis, implying as it does an inflammatory process, for in many of these kidneys there is more of atrophy with secondary fibrosis than of true inflammation. Such terms as granular kidney, contracted kidney, sclerotic kidney, cirrhotic kidney, are employed to describe this form or some modification of the same.

Etiology.—The causes of chronic interstitial nephritis of the secondary type are those already enumerated for the chronic parenchymatous form. The arteriosclerotic kidney has its etiological factor in any of the conditions that lead to general arteriosclerosis—lead, gout, syphilis, alcohol, heredity, severe muscular strain, overwork, worry, etc.

Several years ago Rosenstein wrote that for the overwhelming majority of cases of genuine contracted kidney we know no cause. This statement holds to-day. Yet some facts seem fairly well established. The origin is in many, probably most, cases hæmic, through the presence in the blood of material that acts on the kidney as a toxic irritant. Some of the causes enumerated for acute nephritis might, if long continued in milder degree,

produce the chronic inflammation. Some French writers (Brault) recognize this by speaking of chronic interstitial nephritis as *néphrite par intoxications lentes*. The causes of acute nephritis may also be regarded as occasional causes of this form, for exceptionally an acute nephritis is the definite starting point; a scarlatinal nephritis, for example, passes gradually into the contracted kidney with typical cardiovascular and urinary phenomena, and at death several years later the small indurated kidney is found. Dickinson[1] describes such cases.

Heredity.—A hereditary tendency to chronic nephritis is undoubtedly seen at times. Reference has been made to an example of this in a woman with contracted kidney, whose three daughters and one son show albumin and beginning nephritis, and several of whose ancestors had chronic nephritis. Dickinson saw nephritis in four generations; Eichhorst[2] 5 cases in three generations; Kidd,[3] 7 cases in three generations. A. V. Meigs[4] saw cases in father, son, and three daughters. Pel,[5] in three generations, saw 18 cases, 9 males inheriting from the father, 9 females inheriting from the mother. Frölich[6] reports family nephritis, perhaps hereditary. Tendency to early arterial degeneration is often hereditarily transmitted. In some families this is seen in cerebral hemorrhages; in others as myocarditis or pectoral angina, or again as contracted kidney. Or one member of the family exhibits one manifestation of the disease, *e. g.*, the myocardial, while another has cerebral hemorrhage, and another has chronic nephritis. Not infrequently in one and the same individual there may be manifested not alone the nephritis, but the myocardial or cerebral evidences of arteriosclerosis.

Congenital contracted kidney has been reported by Weigert and by Hellendahl. In childhood chronic interstitial nephritis is relatively rare, yet it has been seen by many observers. Some of these cases—a very small proportion surely—may have developed because of an inherited or family tendency.[7] Sutherland and Walker[8] report interstitial nephritis in infants, and refer to the fact that such nephritis due to syphilis is not unusual.

Carpenter[9] reviews the subject of nephritis in infants, and comes to the conclusion that infantile interstitial nephritis may be produced by toxins other than those of syphilis; possibly toxins of intestinal origin may be the cause in some cases. Nephritis in infants he regards as not infrequent, but as easily overlooked at autopsy unless microscopic examination be carefully made. Occasionally from unknown cause an early arteriosclerosis develops, as in the case described by Egon Rach,[10] of a girl, aged thirteen years, in whom a chronic nephritis with dropsy was followed by hypertrophy of the left ventricle, rigid arteries, and death from cerebral hemorrhage.

Gout is a common cause of chronic nephritis. English physicians are practically unanimous in ascribing many cases of contracted kidney to gout.

[1] *Allbutt's System*, 1897, v, 376.
[2] *Specielle Pathologie*, fourth edition, ii.
[3] *Practitioner*, 1887, vol. xxix, p. 104.
[4] *Transactions of College of Physicians of Philadelphia*, 1883.
[5] *Ztschr. f. klin. Med.*, 38, p. 127; with literature.
[6] *Norsk. Mag. f. Laegevid*, 1904, No. 8.
[7] Heubner. *Ueber chronische Nephritis und Albuminurie im Kindesalter*, Berlin, 1897.
[8] *Archives of Pediatrics*, 1903, xx, 288; also *British Medical Journal*, 1903, i, 959.
[9] *British Journal of Children's Diseases*, iv, 421.
[10] Abstract in *Deut. med. Woch.*, 1907, No. 34, p. 1387.

Some have even gone so far as to regard the kidney of gout as typical of this form of nephritis, and to refer to it in general as the "gouty kidney." There is not such a uniformity in regarding *lead* as the exciting cause of chronic nephritis. Many are inclined to look upon the contracted kidney developing in the course of chronic lead poisoning as due rather to the gouty condition that is so often a sequel of lead poisoning ("lead gout"). Olliver, in 1863, described albuminuria in workers in lead. Since then numerous statistical studies have borne out the truth of this observation, and early nephritis, with general arteriosclerotic changes, is among the well-recognized lesions of lead poisoning. Senator, among 250 cases of chronic indurative nephritis, found 17 caused by lead; Wagner, in 150 cases, found 15 due to lead. Dickinson found 26 of 42 workers in lead with contracted kidney. The fact that lead is found during life in the urine of these patients and in their kidneys after death, as well as the fact that there is often no distinctive gouty manifestation, makes one feel that lead alone without gout may produce chronic interstitial nephritis, although there are workers in lead who have both lead intoxication and gout and later develop nephritis.

Of the influence of *alcohol* in the production of nephritis there is little doubt. But observers differ widely in their estimate as to the importance of alcohol as a causative agent. Probably but a small proportion of typical cases of chronic interstitial nephritis can be traced directly to chronic alcoholism. Christison believed alcohol was the cause of a large percentage of cases of chronic nephritis. Grainger Stewart also refers to the close relationship between intemperate habits and renal cirrhosis. Rayer placed alcohol at the head of the list of causes, and Senator regards it as a potent factor. On the other hand, Lancereaux denies that alcohol is a common cause, and Dickinson believes its etiological influence has been greatly exaggerated. Osler thinks overeating a commoner cause than overdrinking. Strümpell says, while alcohol is certainly a cause of chronic nephritis, it is often so because joined with overeating. Experimentally, little definite has been brought forth to show a direct influence of alcohol in the production of chronic interstitial nephritis. Clinically, as seen by these citations of opinions, the question is by no means settled. It would seem that alcohol is unquestionably an important factor in the production of chronic nephritis, not always through the direct action of the alcohol on the kidneys, but oftener indirectly through perversion of gastric and hepatic function, through induced faulty metabolism, through secondary digestive disorders, through exposures and excesses of various kinds, all the result of alcoholic overindulgence.

Not infrequently chronic interstitial nephritis can be traced to a preceding *acute infectious disease* that was complicated by acute nephritis. Scarlet fever is, therefore, the real cause of some of these cases, the acute process in the kidneys subsiding, but seeming to be the starting point of the chronic inflammation that follows. Other acute infections, *e. g.*, malaria or rheumatic fever, are also incriminated, although many cases reported as due to the acute infectious disease are undoubtedly instances in which a previously existing but unsuspected nephritis has been noted only because of the urinary examination at the time of, or soon following, the infectious process. Slight attacks of tonsillitis may be a cause more often than we have generally supposed. Most of the cases of chronic interstitial nephritis seen in childhood are probably, as Heubner suggests, due to previous infections—scarlatina, measles, angina, pneumonia, intestinal disturbances due to bacteria—

which may have been slight in character and in which no symptoms drew attention to the urine or kidneys.

In this connection one is led to think of the marked acute parenchymatous degeneration so frequently present in these acute infections, of the cellular destruction often seen in this condition and in acute nephritis, of the numerous patches of visceral round-celled infiltration and of focal necrosis, and to surmise that in place of the destroyed cell or in the area of focal necrosis fibrous tissue may be formed and serve as a nucleus for the spread of a local or more extensive fibrosis, in accordance with Weigert's law of primary destruction of specific tissue elements and replacement by newly formed connective tissue. Such origin in some preceding acute infection may explain the development of many otherwise inexplicable cases of chronic interstitial nephritis, as well as of some cases of hepatic cirrhosis and of chronic fibrous myocarditis.

A cause whose influence it is difficult or impossible accurately to estimate and to which reference has already been made in discussing general etiology, is repeated or chronic *gastro-intestinal disturbances* with faulty digestion, and the still more obscure *faulty metabolism* on the part of such organs as the liver, pancreas, or adrenal. Unnatural chemical products may be present in the blood under these conditions, and be the irritating cause of the change in the kidney. In this way alcohol, by disturbing the function of stomach, bowel, and liver, may be an indirect cause of nephritis. So overeating or the eating of rich or improper food, the excessive use of proteids, in short any often repeated dietetic errors, may be conceived of as the underlying causative factor in the production of chronic nephritis. George Johnson thought that degeneration of the kidney was often brought about by long-continued elimination by the kidney of products of faulty digestion. How much influence disturbances in the function of the liver, pancreas, thyroid, or adrenal may have is not clear. Nephritis in connection with hepatic cirrhosis is not uncommon, both perhaps due to the same cause; yet the influence of perverted function of the liver on the kidney, forcing it to eliminate improperly elaborated substances, is not to be underestimated. Caro[1] found nephritis in from five to eight days after experimental thyroidectomy in cats. Diabetics often have albuminuria and true chronic nephritis may develop, possibly from overwork of the kidney; but apparently the condition is due to toxic degeneration of renal epithelium (changes in Henle's loops in diabetes) that if long continued leads to fibrosis. Senator regards diabetes as a not infrequent cause of nephritis. The relation of renal sclerosis and of general arteriosclerosis to perverted adrenal function is still unknown. The sclerotic changes in nephritis and the presence in the blood of such patients of a blood pressure raising substance, as shown by numerous observations, which substance is perhaps identical with the secretion of the adrenal, raise questions of great interest and open the doors for future careful research. Many cases of chronic interstitial nephritis, then, may have their origin in undetected anatomical or physiological changes in other important viscera.

The relative infrequency of this form of nephritis in the warmer climates has been frequently noted. This may be in a measure accounted for by the fact that in the warmer climate there is less exposure to cold, inclement weather, and sudden changes of temperature; the inhabitants consume less

[1] *Mitt. a. d. Grenz. d. Med. u. Chir.*, 1907, xvii, 447.

meat and proteid food, drink less strong alcoholic drinks, and are subjected to less wear and tear through the strenuous life.

The kidney of *pregnancy* may be the starting point of the disease, although some cases regarded as originating during pregnancy undoubtedly have been cases of chronic interstitial nephritis, with an acute exacerbation.

Cardiac disease and chronic interstitial nephritis often co-exist. The relation between the two diseases is not always clearly definable. In many instances the same cause has produced the nephritis and the valvular or myocardial lesion. In other cases primary renal lesion has caused the secondary changes in the heart, the hypertrophied muscle finally becoming incompetent and cardiac symptoms being the most striking feature in the case. In a few cases chronic interstitial changes in the kidney result from an incompetent heart, with its resulting long-standing passive congestion of the kidney (cyanotic induration), together with its accompanying toxic condition of the blood from cyanosis, alimentary disturbances, and faulty metabolism. A direct connection, however, between valvular disease of the heart and chronic interstitial nephritis is seldom to be made out. Localized areas of chronic fibrosis in the kidney often result from renal infarcts that may have their origin in a diseased heart.

Since Gull and Sutton, nearly forty years ago, called attention to the fact that certain diseased conditions affected the entire vascular system as a unit, some cases of chronic disease of the kidney have been regarded as but part and parcel of general *arteriosclerosis*. The causes of the arteriosclerotic kidney would be those of arteriosclerosis in general: old age, heredity, syphilis, lead, gout, alcohol, excessive work, and preceding infectious diseases. Chronic interstitial nephritis is found oftener in males and in those past the age of thirty; the variety spoken of as the arteriosclerotic kidney, in the stricter sense, is rarely seen until after forty-five.

Chronic fibroid changes may take place in the kidney when there is *chronic obstruction* to the outflow of urine, or disease of the pelvis of the kidney. Thus, in stricture of the urethra or ureter, in cystitis and pyelitis this is at times noted. While not in a strict sense of the same type as chronic interstitial nephritis, this "consecutive nephritis" may be here referred to, as it is practically, a fibrosis.

A *traumatic origin* of some cases of nephritis has been alleged. Küster, Edlefsen, Curschmann (the younger), Engel, and others have written concerning it. Orth, in the discussion on Ponfick's and Müller's papers at the Congress in 1905, referred to specimens in his possession showing typical contracted kidney from subcutaneous injury of the kidney. Posner[1] cites a case that came under his own observation in which he believes trauma caused the nephritis. As Posner says, direct injury to the kidney may make it a favorable place for the lodgement of germs or endogenous or exogenous toxins —and the uninjured kidney become secondarily involved. Posner is inclined to include under traumatic causes the mechanical disturbances due to circulatory alterations. Here might also be included Newman's cases of nephritis in floating kidneys,[2] in which condition Newman finds Bright's disease not so very uncommon; and also some cases of obstruction to the ureter with resulting circulatory, nutritional, and fibrotic processes in the

[1] *Deut. med. Woch.*, 1906, xxxii, No. 12, 454.
[2] *Glasgow Medical Journal*, 1904.

kidney. Tornellini,[1] however, finds in rabbits after trauma no interstitial nephritis, but circumscribed zones of connective tissue, *i. e.*, a scar representing necrobiotic areas. He regards trauma in man as probably only one cause, the immediate exciting cause perhaps, but thinks preceding infection or intoxication must already have existed. Trauma causing a contusion of the kidney may be followed by hæmaturia, albuminuria, and cylindruria, and it is not impossible that the rupture of vessels and the destruction of kidney substance may be followed by a reactive inflammation or a genuine nephritis.[2]

Many attempts have been made to produce *experimentally* a chronic nephritis of the type of the contracted kidney. These efforts have met with but indifferent success. The conclusions, too, in some instances are rather hastily drawn, the number of observations too few, and not enough consideration given to the fact that albuminuria and renal disease might have existed in the animals used prior to the experiments. In dogs chronic nephritis seems to be not uncommon.[3] A great number of both organic and inorganic chemical substances have been employed, as well as various microörganisms and their toxins. The results that have been the most nearly constant in the way of a chronic nephritis, and not merely acute or chronic degenerative lesions or those of temporary character, have been brought about by the long-continued use of small doses of the salts of lead. Nearly all of the experimental work has been based on an attempt to alter the condition of the blood by adding to it some substance that would act as a toxic irritant as it came in contact with the kidney, although experiments have also been made by mechanically injuring the kidney or by removing portions of a kidney by operation; and also by altering the viscosity of the blood. Recently, Haven Emerson[4] has done suggestive, although not yet conclusive, work in attempting to produce chronic nephritis in dogs by using means that presumably materially alter the circulation in the kidney, and he argues in favor of circulatory stagnation and defective blood supply to the kidney as potent causes of chronic nephritis, and as capable of being brought about by chemical or mechanical agents. But no experimental work can exactly or even approximately duplicate the conditions that seem operative in the production of chronic interstitial nephritis in man. The influence of heredity, dietetic errors, faults of metabolism, syphilis, many of the infections, the wear and tear of the strenuous life and of excessive mental and nervous strain—all these continuing perhaps for years—cannot be reproduced in experiments on the lower animals. Experimental work will probably, therefore, be more or less unsatisfactory. Bradford[5] in his Croonian lectures on Bright's Disease and its Varieties, reviews the experimental work on nephritis. While showing its great value, he says that there are still lacking many of the conditions found clinically, and that the results (*e. g.*, with nephrotoxins) are often far from conclusive.

After all is said concerning the etiology of chronic interstitial nephritis,

[1] *Vierteljahrsschr. f. gerichtl. Med.*, Band xxxiv, Heft 1.

[2] Cf. Senator, *Berlin. klin. Woch.*, March 16, 1903.; also Engel, *ibid.*, 1903, No. 10.

[3] Cf. Pearce, *University of Pennsylvania Medical Bulletin*, 1903–4, xvi, 217; also Ophüls, *Journal of Medical Research*, 1908, No. 106.

[4] *Archives of Internal Medicine*, 1908, i, No. 5. Here will be found numerous references to experimental nephritis.

[5] *London Lancet*, 1904, vol. ii.

we come back to Rosenstein's statement, already quoted, that for the majority of cases we cannot assign a definite cause. In many cases a combination of causes seems to operate. Undue exposure to inclement weather, overindulgence in the way of food and drink, heredity, with excessive mental and nervous strain, contribute each its share. A peculiar susceptibility may explain why one individual will develop the disease, while another, under what seem to be exactly similar conditions, or even under conditions that would seem more likely to favor the development of nephritis, will escape. It is but another illustration of the fact so often illustrated with regard to other diseases, that what is one man's meat is another man's poison.

Pathological Anatomy.—**Primary Chronic Interstitial Nephritis.**—Almost always the process is bilateral; unilateral chronic interstitial nephritis is extremely rare. There are probably occasional exceptions to this statement (Israel, Senator, Klemperer), and at the very beginning of an acute or even chronic nephritis it is not impossible that one kidney alone may for a short time be involved. But such labored arguments as those of Pousson,[1] striving to prove that unilateral nephritis *might* occur, and therefore does occur not infrequently, are more than offset by statements such as those of Guiteras, who in 500 autopsies on patients with Bright's disease never saw one kidney alone involved, or of Kümmell, who says that in the rich autopsy material at Hamburg no instance of unilateral nephritis has been seen.

The kidneys are small, sometimes unequally so. The single kidney may weigh only fifty or sixty grams, occasionally even less than this; it may be represented by a mere dwarf-like "nubbin" or remnant, although when the process is comparatively recent the size may be but slightly less than normal. The color is variable, but in general is red or grayish red. The fatty tissue about the kidney is unusually abundant and may be quite firmly adherent to the true fibrous capsule. This latter capsule is often quite vascular, and is thickened and raised in uneven manner by the granular elevations of the kidney surface beneath, that alternate irregularly with darker red depressed areas that denote underlying contracting fibrous tissue. This irregularity of the surface of the reddish kidney makes the name raspberry kidney, sometimes applied, appropriately descriptive. When the capsule is stripped off, it is found to be adherent, especially over these depressed regions, and when it is forcibly removed more or less of kidney substance is pulled away with it, leaving a rough, granular, uneven, reddish surface that is quite characteristic. The kidney is hard and cuts with increased resistance. Small retention cysts may be opened on section; or some of them may have been seen under the capsule, or have ruptured when the capsule was removed. The cysts usually contain a pale-yellow, serous, or urinous-looking fluid that is albuminous, perhaps slightly blood-stained, and contains more or less urea. The cut arteries may be plainly seen, and may gape and show thickened walls. The cortex is narrowed; it may measure only 1 mm. In some places the pyramids lie almost immediately under the capsule. The pyramids, although absolutely shrunken, seem by comparison with the contracted cortex to be large. The cut surface is reddish in color, with a liberal mottling of gray due to the connective tissue that at times is seen as whitish masses or bands that sometimes extend from the cortex

[1] *Zeitsch. f. Urologie*, 1907, i, 853.

into the pyramids. Beneath the depressed areas on the surface, with the naked eye or a low power lens, may be seen masses of fibrous tissue often extending quite a distance into the kidney. The lighter areas that form the projections on the surface represent the more nearly normal tissue, some of which, in reality, may be compensatorily hypertrophied. There is commonly an abundance of fat in the renal pelvis.

The microscope reveals a general increase in the fibrous tissue, a thickening of the vessel walls, destruction of glomeruli, and more or less degeneration of the renal epithelium. The cortex, especially the labyrinth, shows the most marked change, although the lesions are not uniform in their distribution. Even in the areas between the labyrinths that are more nearly normal the epithelium often shows some fatty degeneration, and foci of round-celled infiltration may give evidence of an early stage of the indurative process.

Malpighian Bodies.—The glomeruli are strikingly altered. Many are destroyed, being represented by structureless hyaline masses. Others show the remains of the capillary tufts in the shape of homogeneous or granular balls in which a few nuclei may still be seen. Again the capillary tuft, the capsular space, and even the epithelium lining Bowman's capsule may appear normal, but a richly nuclear fibrous ring, often quite broad, surrounds the entire Malpighian body in concentric layers, or the ring may be dense and poor in nuclei.

The capsular space may be obliterated, the capillaries and capsule being adherent, or the space may be widened. This widened space may be the result of obstruction to the outflow of urine from obliterated tubules, the dilatation being on the order of a retention cyst. Compression of the tuft may thus result. Nuclear proliferation is often seen in the tuft. Especially in the small projections on the surface of the kidney, that give it its granular appearance, large compensatorily hypertrophied Malpighian bodies may be seen showing little or no pathological changes. In places the bodies, from atrophy and contraction of intervening tissue, are closer together than in the normal kidney.

It is easy to understand how the glomerular function is seriously interfered with by the circulatory disturbance due to the endarteritic change in the afferent vessels, as well as to the hyaline degeneration in the wall of the capillary tuft, the compression due to the growth and contraction of fibrous tissue in the same, and to the encircling and constricting fibrous band surrounding the Malpighian body as a whole. And one may understand also how the integrity of the tubular epithelium may be impaired owing to these glomerular changes that must result in serious interference with the circulation in the tubular wall, insufficient nutrition, and largely account for cellular atrophy and functional inactivity. By some the glomerular changes are regarded as primary, the tubular and interstitial being the result of glomerular lesions. Some of the glomerular changes, however, *e. g.*, the cyst-like dilatation of the capsule, seem secondary to tubular trouble, and this, in turn, to contraction of the interstitial fibrous tissue. Perhaps the most correct conception is to regard the process as from the first more or less diffuse, and to look upon a change in one part as necessarily leading to change in another, after the manner of the vicious circle.

Tubules.—Atrophy is more or less marked. Many tubules are narrow, lined with small flat or cubical cells, and quite collapsed. Others, from blocking of their excretory ducts, have become dilated with hyaline-looking

or granular and fatty cells lining them, or have even formed retention cysts of various shapes and sizes. These cysts sometimes coalesce so as to resemble compound cysts. In some tubules all the cells have disappeared, leaving bare the basement membrane. The lumen of the tubules that are still patent may contain a few hyaline or granular casts, some of the atrophied cells, perhaps granular debris, and an occasional leukocyte or red corpuscle. In the areas that show compensatory hypertrophy, the tubules and cells at times seem larger than normal or even increased in number, reminding one of the somewhat similar, almost adenomatous increase of the healthy liver cells in hepatic cirrhosis. The tubules in these areas sometimes show unusual turns and twists, much as in an adenoma. Their epithelium may show fatty degeneration.

The Vessels.—An endarteritis or even a mesarteritis can usually be made out, the intimal thickening often perceptibly narrowing the lumen. The smaller intertubular vessels are especially involved and are often entirely obliterated. This must, by causing interference with the blood flow, increase the pressure in the glomerular capillaries. This has been given as one explanation of the polyuria of chronic interstitial nephritis.

The degree to which different arteries are altered varies, some showing marked thickening in the outer and middle coats, but especially in the subendothelial layer, others but slight changes. The sclerosis is sometimes patchy, even in the individual artery, one portion of the circumference showing an extensive lesion, while the remainder of the ring is nearly normal. The lumen of the thick-walled vessel may be nearly normal, the pipestem-like artery gaping with wide-open mouth as it is cut across, while in other vessels the caliber is gradually narrowed until it is quite obliterated. Dickinson[1] found by actual measurements that the caliber of the primary arteries was not altered even though the walls were thick. The obstruction to circulation, as he proved, was in the minute arterioles and in the capillaries, many of which were entirely destroyed. The roughened intima with the sluggish current that must flow through some of these vessels favors thrombosis, and thrombi may be seen in some of the vessels, such as the smaller interlobular arteries. From destruction of vessels there results a compensatory collateral venous circulation. Part of the blood escapes by way of the vessels of the renal capsule and the perirenal fat. Other channels are described by Thoma[2] and by Buhl.[3]

The Interstitial Tissue.—This is increased. The thick, fibrous bands surrounding the Malpighian bodies present perhaps the most striking picture, but the newly formed connective tissue rich in nuclei, or the old scar-like bands and masses, may be seen nearly everywhere, between the tubules, in the pyramids, and about the vessels, and especially running down into the labyrinth from the surface depressions and sending out bands of fibrous tissue that encircle and ensnare the healthy tissue on either side. Masses of round cells representing young contractile tissue may be seen especially under the capsule and around the glomeruli and vessels, from which points the process extends downward and out into the intertubular tissue. The contraction follows so soon, that even though this nuclear

[1] *Lancet*, 1895, ii; also *Medico-Chirurgical Transactions*, vol. xliii.
[2] *Virchow's Archiv*, 1877, vol. lxxi.
[3] *Mittheilungen aus d. path. Institute in München*, 1878.

overgrowth, as it has been termed, be excessive, the kidney is always small. The contraction of this fibrous tissue warps and deforms the kidney not only macroscopically, but also microscopically, so that it is often difficult to get one's bearings and to know exactly what altered structure is for the time under examination and just what relation it bears to surrounding structures. In places, little or no relic of renal structure is to be made out, the section showing merely dense fibrous tissue. That changed anatomical conditions and perversion of function in the tubules result from this process may be easily understood. Sometimes calcification is found in this adventitious fibrous tissue.

Secondary Contracted Kidney.—This is seen in its earliest stage in some of the kidneys of chronic parenchymatous nephritis, the large white kidney, in which a few depressions on the surface and a beginning hardening from fibrosis show that had death been deferred for several months the kidney of secondary contraction would, in all probability, have been present. This kidney in reality seems much like a cross between the kidney of chronic parenchymatous nephritis and the contracted kidney. It is pale in color, of normal or diminished size, its capsule thick, the surface granular. The kidney feels firm to the touch. The cortex is narrow and pale. Fibrous tissue is seen in greater or less abundance, the glomeruli are in general small, surrounded by bands of fibrous tissue and at times have undergone atrophy and completely disappeared. Hyaline degeneration of the epithelium of the tubules is pronounced or the cells may have entirely disappeared, leaving the tubule denuded and seemingly dilated. Some of the dilatations are on the order of retention cysts. The vessels may show mural thickening. The picture in advanced cases is not unlike that of the chronic interstitial nephritis, and the loss of tubules and glomeruli with the contraction of the fibrous tissue explains the small size of the organ and its hardness. Bradford[1] believes the contracted white kidney is a distinct entity and not related, on the one hand, to the large white kidney or, on the other, to the truly granular kidney.

Arteriosclerotic Kidney.—This form is a not uncommon postmortem finding in those past the middle years of life, and especially in those who, from excessive mental, nervous, and physical work, from the too liberal indulgence in rich food and drink, or from hereditary influences, have had operating upon them for many years the causes favoring the development of general arteriosclerosis. The arteriosclerotic kidney, as already stated, is regarded as but one manifestation of a widely distributed vascular sclerosis, so that at autopsy, cardiac hypertrophy, thickened cerebral vessels, with perhaps rupture and hemorrhage, are commonly met with. The conception of the disease is that of a simple non-inflammatory atrophy. Vascular thickening, with slowing or shutting off of blood current, leads to nutritional defects, anæmia, and necrosis, with fibrous-tissue development in place of the destroyed parenchymal structures. Yet the combination of inflammatory, sclerotic, and atrophic changes is common and so complex that it is often difficult or impossible to make a sharp differentiation, even postmortem, between the purely degenerative and atrophic lesion and the inflammatory, or to tell which was the primary one. The kidney itself is usually reddish or grayish red in color, and but slightly smaller than normal. In long-standing cases,

[1] Croonian Lectures, *Lancet*, 1904, ii.

however, there may be extreme reduction in size. It is firm to the touch, and the capsule that is not much thickened may often be stripped off readily without bringing away much of the kidney substance. The surface of the kidney is smooth, although here and there the local cortical atrophy may be revealed by a depressed area, and the presence of cicatricial tissue in such an area will be revealed not alone by the microscopic examination, but by the fact that the capsule is bound to the kidney at this point by fibrous adhesions. A few subcapsular cysts are occasionally seen.

The hard cut surface may show gaping vessels; the cortex is narrow. Some of the changes seen on microscopic examination are in many respects similar to those decribed under primary chronic interstitial nephritis. Many of the smaller vessels show intimal thickening. The small-celled infiltration is, however, lacking or but slightly marked, as about the vessels and Malpighian bodies, in which case some incline to the view that a secondary inflammatory process has been added to the primary atrophic one. There is less striated connective-tissue thickening about Bowman's capsule than in the inflammatory form. Many of the Malpighian bodies are destroyed. In others, the capillary tuft may be obscurely outlined as to its its details, being represented by a homogeneous, hyaline mass, with a few scattered nuclei still visible. The capsule proper may be thickened, on its inner side it may be denuded of its epithelium, and it may even have contracted down so as to be in immediate touch with the tuft, the capsular space thus being obliterated. In this form of renal disease, as in most others, there is seen that remarkable irregularity in the distribution of the lesion—the "patchy" distribution—to which attention has already been directed. This may result in normal glomeruli being seen side by side with those quite markedly altered or even completely destroyed.

Many tubules will appear normal. In others, however, the atrophy is manifest in the small size of the cells, the loss of their normal markings, their flattened shape, or their total destruction. Often the narrowed tubule has collapsed, leaving a cord-like mass to represent it, or possibly a small retention cyst. These cysts may contain a clear fluid with masses of colloid-like material. The same colloid-like masses, occasionally a hyaline or granular cast or granular and fatty epithelial cells, may be found in some of the tubules.

Among findings *in other organs* that are met with quite regularly must be mentioned the *hypertrophy of the heart and the sclerosis of the arteries.* Left heart hypertrophy is the rule, and is always present before enlargement of the right ventricle. In advanced cases and especially in cases where dilatation of the left heart has occurred leading to mitral insufficiency, there may be right heart enlargement, and the whole heart is truly bovine. The aorta and smaller vessels show more or less advanced sclerotic changes. Even when the aorta may not be markedly involved, the smaller arteries, *e. g.*, in the spleen, will usually exhibit some degree of thickening of their walls. Exceptionally, typical contracted kidney has been found unaccompanied by arteriosclerosis or cardiac hypertrophy. Roth[1] reports six such cases. Death was generally from uræmia. In most of the cases blood pressure had been low. The causes of these cardiovascular changes are discussed elsewhere.[2]

[1] *Virchow's Archiv*, 1907, Band clxxxviii, 527.

[2] For a brief *résumé* of the subject one may consult Senator, *Deutsch. med. Woch.*, 1903, xxix, p. 1.

Such accidental or complicating conditions as cerebral hemorrhage or dropsical accumulations, where toward the last there has been cardiac insufficiency, are often seen. The alimentary tract is usually in a state of catarrhal inflammation, and uræmic ulcers may be present. Devic and Charvet[1] review the entire subject of *uræmic ulcers* and find them to be present oftenest in the chronic interstitial nephritis especially when uræmic symptoms are prominent. Hemorrhagic infiltration, follicular or linear erosions, may result in deep ulcers that show little tendency to heal, and are prone to bleed or to perforate. Accumulation of toxins in the body, the influence of accidental microbic complications, together with vascular changes and consequent circulatory disturbances, are their cause. Dickinson's[2] lectures also contain a comprehensive discussion of these ulcers.

It will be in place to mention here some recent experimental work on the pathological anatomy of nephritis, the bearing of which on the physiology of several of the viscera, as well as on the pathogenesis of nephritis, the questions of blood pressure, etc., will at once be seen. While far from conclusive, it is surely suggestive, and should arouse interest in further experimental work of this kind. Laederich[3] finds that not only in animals which die as the result of a sudden suppression of renal function, as by operative removal of the kidneys, are *hepatic* lesions due to toxic degeneration regularly found, but in cases in which a gradual renal insufficiency is brought about, certain peculiar hepatic cellular changes are found (état clair avec surcharge glycogénique), which condition he describes and illustrates by plates. This condition of renal insufficiency, if continued for a long period, finally leads to a periportal sclerosis. One sees, therefore, the interdependence of these two eliminating organs. The kidneys and the liver, the principal eliminating organs of the body, are closely related by a physiological synergy and a pathological solidarity. Hepatic insufficiency can determine renal changes; experiment shows that renal insufficiency may induce reactions and lesions in the liver.

Beaujard,[4] in a critical review, describes the *suprarenal* lesions in nephritis, as found by several observers. Cortical hyperplasia is common in interstitial nephritis. One of three explanations is possible: (1) The suprarenal hyperplasia may be the cause of the hypertension and independent of the nephritis; (2) the suprarenal hyperplasia is the cause of the hypertension, but it itself is produced by the nephritis; (3) the suprarenal hyperplasia is a reaction to the chronic auto-intoxication provoked by the nephritis, along with hypertension, but is not the cause of the hypertension. Darré[5] shows experimentally that in chronic nephritis there is, apparently from resulting intoxication, hyperplasia of the cortical portion of the suprarenal gland, with an apparent increase in function. This function Darré regards as an antitoxic one. These observations do not settle the question as to a possible relation between the hypertension of nephritis and the suprarenal. The hypertensive element of the suprarenal is supposed to emanate from the medullary rather than from the cortical portion.

[1] *Revue de Méd.*, 1903, xxiii. [2] *British Medical Journal*, 1876, i.

[3] *Des Modifications du Foie consécutives aux Altérations Rénales (Étude Expérimentale)*, Paris, 1907.

[4] *La Semaine Médicale*, 1907, No. 20.

[5] *De l'influence des alterations du rein sur les glandes surrénales, Thèse de Paris*, 1907.

Wiesel,[1] however, has found medullary hyperplasia in the adrenal in a case of subacute nephritis. He does not, however, interpret this as necessarily the cause of hypertension but rather as a possible result or concomitant of cardiac hypertrophy.

Symptoms.—Chronic interstitial nephritis is often entirely unsuspected until some sudden uræmic outbreak, or perhaps an apoplectic seizure, leads to an examination of the urine; or the disease may be accidentally detected in the course of a life insurance examination, the applicant regarding himself as in perfectly good health and being entirely free from symptoms. On the other hand, the disease may, for a long time, be rich in symptoms and the cause of years of ill-health and semi-invalidism. There is no one type of the malady. The picture presented is a bizarre one and subject to great variations.

The onset is generally insidious, therefore the date of its inception is unknown. What may perhaps be called a typical case is seen in one of middle years, who begins to fail somewhat in strength, is annoyed by headache or dizziness, has anorexia and other dyspeptic symptoms. Possibly he has noted a little polyuria, and has remarked that he is obliged to rise frequently at night to empty the bladder. For these rather indefinite symptoms he consults a physician, who finds him slightly anæmic, with a heart enlarged, with blood pressure high, and with the urine increased in amount, of low specific gravity, and containing a trace of albumin with a few casts. Possibly at this time retinal changes may be noted. Œdema is conspicuously absent. The disease, however, in spite of care on the part of the physician and the patient, makes steady, although perhaps very slow, progress, with many ups and downs. Later, evidence of cardiac incompetence is manifested, with the usual dyspnœa, palpitation, and œdema; this failure on the part of the heart, uræmia, or possibly cerebral hemorrhage may be the cause of death. But as has been said, there are many variations, and with the multiform manifestations of uræmia, the numerous sequelæ of cardiovascular incompetence, the frequent intrusion of complicating maladies, the possible combinations are almost numberless, so that any clean-cut clinical picture of the disease cannot be drawn. The conditions that stand out most prominently and that form the basis of the diagnosis are the cardiovascular changes, the urinary findings, and the uræmic manifestations. These will be discussed somewhat in detail together with other symptoms of relatively minor importance.

The Urine.—Just when the urinary changes begin to manifest themselves is seldom definitely known, but by the time a diagnosis of the disease is possible the urine, as a rule, shows the following characteristics. It is increased in amount, from 2000 to 4000 cc. being commonly passed in twenty-four hours, although much larger amounts are not infrequently seen. Bartels watched the urine of one patient for a month, and found the daily average amount to be 3350 cc. The nocturnal urine is often greatly increased in amount. Even before polyuria is manifest, frequency of urination may be noted. To this frequent urination Dieulafoy has given the name pollakiuria, and he believes that it often precedes a polyuria. His rather indefinite explanation of this symptom makes it depend upon an irritable condition of the bladder rather than upon any change in

[1] *Wiener med. Woch.*, March 30, 1907.

the kidneys strictly speaking, or even any change in the urine; and he further says that this pollakiuria is sometimes, particularly in women, or where it is a late manifestation, attended with considerable pain. As a rule, when there is an increased amount of urine, together with an increase in the frequency of micturition, the amount passed with each emptying of the bladder is considerable, although in some instances the product of each micturition is no more than is usual, or it may be even rather small in amount. Such frequency of urination is often noted at night, and when it occurs in a man beyond middle years is oftentimes looked upon as due to irritation from an enlarged prostate gland.

The urine is light in color, slightly acid in reaction, and the specific gravity less than normal. Specific gravities of 1005 to 1015 are very common. This low specific gravity, as Traube pointed out, is not influenced as much by profuse sweating, diarrhœa, and vomiting as is the urine of health. Seldom even when congestion is added by reason of a weak heart has the urine a specific gravity over 1016, is it dark colored, or has it a rich sediment of salts (Stern). The total amount of solids for the twenty-four hours may be practically normal. The percentage of solids, as, for instance, of urea in a single specimen, is naturally low. When the heart fails, and blood pressure is lowered, the total amount of urine is usually diminished, and with this there is a decrease in the total amount of solids. The sediment, even when the urine has stood for a long time or has been centrifuged, is quite scanty. In this sediment a few crystals of calcium oxalate or of uric acid may be found. Examination also shows a few epithelial cells and an occasional leukocyte, many being lymphocytes,[1] with perhaps a few stray red blood corpuscles.

The amount of blood, however, may be much greater, and hemorrhages of magnitude have been noted in some instances. Larger amounts of blood occur with an acute exacerbation. Sometimes a tendency to recurrence of the hemorrhages is seen. The exact relation of some cases of so-called essential hemorrhage from the kidney, or renal hæmophilia, to chronic nephritis is not clear. Israel[2] and Askanazy[3] think paroxysmal congestive attacks will often explain it. Kusomoto[4] finds rupture of vessels in the renal pelvis as the cause. Many writers of late believe not a few of the supposedly essential hemorrhages—hemorrhages without anatomical lesion—would prove to be, if studied more carefully as to cardiovascular findings, retina, casts, and subsequent history, instances of chronic nephritis. Many such hemorrhages are from one kidney, and cease under nephrotomy.[5] Kapsammer[6] also, in his recent work on the kidney, speaks emphatically against an essential hæmaturia; there is always some lesion, often a chronic nephritis.

In some cases the hemorrhage is so severe as to suggest the possibility of malignant disease of the kidney, particularly when it occurs in a patient who

[1] Cf. Senator, *Virchow's Archiv*, Band cxxxi; also Schnütgen, *Berliner klin. Woch.*, 1907, No. 45.

[2] *Mitt. a. d. Grenz. d. Med. u. Chir.*, 1900, p. 471; also *Deutsch. med. Woch.*, 1902, No. 9.

[3] *Zeit. f. klin. Med.*, 1906, lviii, 145.

[4] *Deutsch. Arch. f. klin. Med.*, lxxxix, 405.

[5] Cf. H. A. Fowler, *New York Medical Journal*, November 25 and December 2, 1905, with extensive bibliography.

[6] *Nierendiagnostik und Nierenchirurgie*, Wien, 1907, ii, 338.

is much emaciated, and who shows a fairly marked secondary anæmia. Hyaline and granular casts, the latter sometimes small, sometimes broader, nearly always rather pale in color, are present in moderate numbers.

There is no question that occasionally patients with chronic interstitial nephritis pass urine which is free from albumin. Postmortem, the renal lesion may be sufficiently distinct, yet no albumin and no dropsy have been noted during life (Stewart). These cases are, however, quite rare, and many of the instances in which chronic interstitial nephritis has been diagnosed, but no albumin found in the urine, are cases of arteriosclerotic kidney. Yet in some patients who have unmistakable primary chronic interstitial nephritis albumin may be absent after periods of prolonged rest, as, for instance, in the urine passed on first rising in the morning. Nearly always there is serum albumin. Oftentimes, in well-marked cases, the amount of albumin is slight, there being but a faint trace. The total amount for twenty-four hours is usually from one to five grams. Later in the history of the disease, and particularly when there is beginning failure on the part of the heart, the amount of albumin is decidedly greater, and in many instances the amount varies very much, being greater when there has been overeating, undue excitement, exposure to cold, etc.; and with exacerbations the amount of albumin will very materially increase. So, too, the albumin is oftentimes very considerable because the case is, as has already been stated, rather one of chronic diffuse nephritis than in the stricter sense one of the interstitial variety. Albumose is occasionally present in considerable amounts. The exact significance of this is not clear. It is said in some instances to precede the appearance of albumin in the urine in chronic nephritis. The molecular concentration of the urine is diminished; the freezing point is, therefore, nearer 0° C. than normal.

In the arteriosclerotic kidney the urine may be free from albumin or show albumin only occasionally. The urine is, however, usually increased in amount, with the specific gravity nearly normal or slightly less than normal. With the centrifuge a few casts can usually be found. Excess in food, exposure to cold, over-indulgence in drink, may cause an increase in the number of casts and a small amount of albumin to appear in the urine.

Cardiovascular Changes.—The exact time at which the changes in the heart and vessels begin is seldom known in a given case. Senator is firm in his belief that he has seen albumin in the urine with polyuria for a long time before cardiovascular changes have made their appearance. In practice, however, it is a rare thing to find a case of chronic interstitial nephritis permitting of diagnosis in which the cardiovascular changes are not more or less well pronounced. The importance of recognizing these changes cannot be overestimated. It has frequently been said, and with much truth, that the cardiovascular changes in chronic interstitial nephritis are of fully as much importance from the standpoint of diagnosis as the study of the urine.

The heart is increased in size, and may be truly "bovine." The enlargement is chiefly in the left ventricle, the apex being displaced downward and to the left. It is oftentimes found as low as the sixth interspace, and may reach to the left anterior axillary line. The right heart may be pushed to the right so as to simulate enlargement, or later there may be a real enlargement of the right ventricle, that is, a general cardiac hypertrophy. False conclusions may sometimes be reached as to the existence of

cardiac hypertrophy because of emphysema, which may conceal the true size of the heart. The apex impulse is usually strong, rather diffuse, and heaving. The first sound at the apex may be loud and booming, although it is sometimes muffled. The closure of the aortic valves is accompanied by an accentuated, ringing tone. This is one of the most important signs, and it alone, in the absence of other causes for its presence, should hint at the existence of chronic nephritis. The closure of these valves may be so sharp as to give rise to a little shock that is clearly palpable by the flat hand placed over the aortic region. It is difficult to understand Dickinson's statement that the pulmonic sound is the more accentuated in chronic interstitial nephritis. With the greatly enlarged heart the point of maximum intensity of the aortic closure sound is often a little lower down and closer to the midsternum, or even to the left sternal border than is normal, but, as a rule, it is the aortic second sound that is the more accentuated. In many cases the loud, ringing, aortic closure is quite plainly heard at the apex. All these signs undergo many modifications when dilatation has occurred. Then the impulse of the heart may be feeble and wavy; the murmur of mitral regurgitation develops at the apex; gallop rhythm, doubling of the first tone, embryocardia, with irregularity of the action of the heart, may also appear, and naturally dyspnœa, cyanosis, and dropsy are also manifest.

In fact, a difficult problem is presented to the physician, if he happens to see the patient for the first time late in the course of a chronic interstitial nephritis, to tell whether the disease is primarily cardiac or renal. At this time a presystolic murmur somewhat like that of mitral stenosis is said by Bradford to be present. This, however, has not attracted general attention.

The peripheral vessels generally show changes. The arteries are tortuous and the walls frequently thickened. The tortuous and plainly visible temporal artery may give a hint as to an underlying renal disease. The blood pressure is increased and the tension is high. The vessel is often thickened; the pulse has a hard, incompressible, cord-like feel. It is difficult to estimate accurately the blood pressure by the finger alone, for one often finds to one's surprise that a pulse that is without great fulness, and that seems rather small, is in reality a pulse of high tension, as is proved by the use of the sphygmomanometer. This is an instrument of extreme value in the study of renal conditions, not only in giving us help in the matter of diagnosis, but being of great value in the way of prognosis and of showing the results of therapy. Systolic blood pressures in chronic interstitial nephritis are very frequently over 170 mm. Hg., and in the more serious cases and late in the history of the disease the pressure rises to 220 or even considerably over this. Sphygmographic tracings generally show a rather gradual ascent and a blunt or square apex. With a failure of the heart there is naturally a fall in blood pressure. The pulse under these circumstances will be smaller and is frequently irregular. Some phenomena of nephritis depend in part, at least, on this high blood pressure and on the hypertrophy of the heart. Among these might be mentioned headache, dizziness, and hemorrhages, which depend in a measure upon the cardiac hypertrophy and high blood pressure, together with the degenerative changes that have taken place in the vessels.

For many of the phenomena of chronic interstitial nephritis an explanation is offered by *uræmia*. These toxic symptoms may be mild and of long

standing, the so-called chronic uræmia; or they may be brusque in their onset and malignant in their severity, as in sudden severe headaches, convulsions, and fatal coma, the acute uræmia. These various symptoms should be looked at from the point of view of a toxæmia, but for purposes of description it seems better to discuss symptoms referable to the different organs of the body, even though they may not all of them be in a strict sense uræmic, and to make no attempt to draw a very sharp—an artificially sharp —line between the acute and chronic uræmic phenomena.

One hardly knows where to begin the description, for in practice patients come to the physician with a most promiscuous variety of complaints, one organ or system of organs showing perversion of function in one individual, another in another. One patient consults his physician because of dyspepsia, another for polyuria; or it may be for pruritus, poor vision, headaches, dizziness, diarrhœa, cough, dyspnœa, or nosebleed.

Many come because they are "run down." They have lost in vitality, lack energy, seem listless, cannot endure physical or mental strain as formerly, and have lost in weight. Their friends have remarked on a change in appearance. This condition of malnutrition, due to chronic intoxication, is revealed not alone by these subjective complaints, but by the examination of the patient. He appears worn, tired, often anxious. He shows some emaciation. His color is pale or sallow, at times cachectic enough to make one fear the existence of a malignant growth.

The *blood* shows an anæmia of the secondary type, and the hæmoglobin is often around 60 to 70 per cent. Hydræmia is rarely present during the earlier stages of this form of nephritis, as in other forms of Bright's disease, and the specific gravity of the blood will be nearly normal.[1] Late in the disease, when the heart has failed, the blood condition is more of a mixture of anæmia, hydræmia, and cyanosis. The freezing point of the blood is generally normal, —0.57° C., until late, when severer uræmic symptoms appear; then it is lower, —0.59° or —0.61° C. Schur and Wiesel[2] found that the blood serum, *c. g.*, even well diluted, of nephritics with high blood pressure would dilate the pupils of the enucleated eye of a frog that was immersed therein. They suggest that this goes far toward proving the presence in the blood of suprarenal extract—adrenalinæmia—for adrenalin will not only raise blood pressure, as is well known, but will, as Ehrmann[3] showed, act as a mydriatic upon the enucleated eye of the frog. Schlayer,[4] however, from Romberg's clinic, while not entirely denying the facts, says more proof must be offered that the substance in the blood with the hypertensive and mydriatic qualities is really adrenalin, and brings forward some experimental work that seems to go far toward disproving the identity of this substance and adrenalin. In the later stages of the disease, when the patient has suffered for a long time from gastro-intestinal disturbance, such as nausea and vomiting, from dyspnœa, pain and loss of sleep, and when the heart's action is poor, the evidence of malnutrition is often very pronounced, and the sallow, haggard, emaciated, bedridden patient, with his anxious look, dyspnœa, tortuous, visibly beating temporals, makes a picture showing the ravages of a disease

[1] Hammerschlag, *Zeit. f. klin. Med.*, 1892, xxi, 491.
[2] *Wiener klin. Woch.*, 1907, No. 23.
[3] *Archiv f. exper. Pathol.*, Band liii.
[4] *Deutsch med. Woch.*, November 14, 1907.

as relentless in its progress and as destructive of health as carcinoma or tuberculosis. And yet it is remarkable how, early in the disease, many persons, and especially adults, may for years preserve an outward appearance of health, florid of countenance, with firm musculature, springy step, and active mentality. Some of the patients are plethoric and corpulent.

Digestive disturbances sooner or later make their appearance. A loss of appetite, distress after eating, flatulence, coated tongue, occasional feelings of nausea, are common complaints, even early in the course of the disease. Some say (Bartels) that there is a special repugnance to meat; this the writer has not noticed. Later, all these symptoms become aggravated; anorexia is marked, the tongue is coated, the breath foul; food, unless very carefully chosen, causes nausea or vomiting. Dickinson refers to one of his patients in whom vomiting was excited even by the sound of the dinner bell. At times vomiting may come on in a manner almost explosive, much as in cases of cerebral disease, and in some instances it may be a question how much of the nausea and vomiting is due to central irritation, "nervous vomiting," so called, and how much is due to a local condition of chronic gastritis that so often accompanies a nephritis, or to local irritation from the attempt on the part of the body to eliminate urea or its decomposition products, and perhaps other urinary constituents through the avenue of the stomach, *i. e.*, vicariously, for the kidney. Epigastric pain may be complained of; hiccough may be annoying. At times a severe stomatitis is seen, and salivation is sometimes disturbing. Thirst may be extreme, especially when there is marked polyuria. The fœtid odor to the breath is at times so pronounced and so characteristically urinous (ammoniacal; trimethylamin, Senator) as to be of suggestive help in diagnosis. It is usually an indication of extreme toxæmia, and is of bad prognostic import.

The bowels may be constipated or may continue regular. Yet looseness of the bowels is apt to occur as a sequel of the faulty gastric digestion just mentioned. Diarrhœa independently of a disordered stomach may be annoying and weakening. Diarrhœa in general is to be regarded as due to toxæmia, to the chronic catarrhal inflammation of the mucosa so common in nephritis, as secondary to gastric disturbance, or as the result of local irritation due to efforts at vicarious elimination on the part of the intestine. At times the stools are more frequent at night than during the day. The presence in the intestine of the so-called uræmic ulcer may explain an intractable nephritic diarrhœa.

Respiratory symptoms are not infrequent. Catarrhal bronchitis is common. This is apt to be chronic, with especial exacerbations in cold weather. Later, when the heart fails, passive congestion aggravates the condition, and the rales, both dry and moist, are more numerous, especially at the base of the lung, and the cough may be more productive.

Dyspnœa in contracted kidney is common, although the pathogenesis is by no means simple. In some instances a more or less continuous dyspnœa is present, yet aggravated by exertion, seemingly a dyspnœa partly uræmic, yet in a measure cardiac. Again, it seems wholly cardiac, and is noted only on exertion, the heart being incompetent when any unusual demand is made upon it. Most characteristic, however, is a dyspnœa that is paroxysmal and very often nocturnal. The sufferer is wakened with a feeling of oppression and weight in the chest, sometimes a distress that is painful and almost anginal in nature. He sits up in bed and leans forward,

in order to breathe the more easily. His labored breathing is as in asthma, the piping and whistling sounds being made out on thoracic auscultation, or even heard at a distance. The attack may be over in a few minutes, to be repeated later in the night. Sometimes relief comes with the raising of thick mucus or a thinner, watery fluid from the bronchi. What part is played by the heart in these cases, what by spasm of the bronchioles excited by toxins, what by the central nervous system irritated by the uræmic poison is not clear. It is often spoken of as a "cardiac asthma," occurring in the course of chronic interstitial nephritis when the heart is on the verge of failing. But surely the uræmic element cannot be eliminated in the consideration of many of these cases.

Somewhat resembling the asthma-like paroxysms and sometimes complicating them is a sudden acute œdema of the lungs. Dyspnœa is extreme, cyanosis is marked, and the pulse may grow feeble. The chest shows fine and coarse rales of every description, although chiefly of the moist variety. There is a persistent cough and an abundant, foamy, serous, sputum, often bloody. In how far this condition is congestive and due to a weak heart, how far uræmic-toxic or even inflammatory, is not clear. It is at times a serious condition and may be an immediate cause of death. An acute œdema of the glottis may also occur, even when œdema is not present in other parts of the body. This may be so threatening as to demand tracheotomy or other radical measures for prompt relief, failing which, death may be caused by suffocation.

When other symptoms of uræmia are marked, as when the patient is stupid or even comatose, Cheyne-Stokes respiration is often present. But it may also be noted at times when the severer uræmic symptoms seem remote. The patient may be feeling fairly well and engaged in his regular occupation. The heart muscle, too, may be doing what seems to be good and efficient work, yet breathing of this type may be present. At times it may precede a fatal result by many months; it may even be present for a time and disappear. It is often a cause of no inconvenience to the patient, and is only noted by the careful physician at his routine examination, or an observant wife may describe the long pause in the breathing of the husband as he sleeps, and even tell how many seconds elapse before the peculiar rhythmic respiration begins again. In other cases the periodicity in the breathing is strikingly apparent to the patient, and the deep respirations are quite annoying. Osler mentions a patient who could be fed only in the period of apnœa.

Among causes of dyspnœa should, of course, be mentioned such conditions as complicating pneumonia or pleurisy. An insidious hydrothorax, too, is readily overlooked. This, especially if bilateral, is often a cause of dyspnœa; if not the sole cause, at least an auxiliary one. It is astonishing how, in some instances, the dyspnœa that has been explained and treated on the supposition that it was purely uræmic, cardiac, or central, disappears when the pressure of the pleural transudate is removed by paracentesis. Pericarditis or hydropericardium should also be referred to as an occasional cause of dyspnœa.

Hemorrhages from the larynx or bronchi may occur, and these may be but one manifestation of a tendency to bleeding that is more or less widespread in this disease. In some instances a genuine hemorrhagic diathesis seems to develop, with bleeding from the gums, into and under the skin (purpura),

and from various mucous membranes. Oftener, however, the hemorrhage does not seem to depend so much on a general blood change (hæmolytic) as upon the degenerative alterations of the walls of the smaller vessels, leading to their weakening and their giving way under the strain to which they are subjected, because of the high blood pressure. Rupture of cerebral vessels, as is well known, is common in contracted kidney, a goodly percentage of cases of cerebral hemorrhage being due primarily to an underlying nephritis. This may occur even in the young nephritic. Dickinson had such an accident in a girl aged twelve years. Most often the intracranial hemorrhage is into or near the internal capsule, although it may be into other regions of the brain or into the meninges.

Nosebleed is very common, and when not clearly explicable on other grounds should always lead to an investigation as to possible nephritis. It may be slight and oft-recurring. Yet it may be severe enough to demand plugging the posterior nares. Strümpell and Senator have each seen two fatalities from this form of hemorrhage. Hemorrhage from the stomach, the bowel, the uterus, the kidney, may occur. Hemorrhage into the tympanic cavity or into the membrana tympani may cause deafness; and retinal hemorrhage, to be referred to later, may cause disturbance of vision. These various hemorrhages, while commoner in advanced chronic interstitial nephritis, may be among the early symptoms. The existence of any renal disease, or even of any disease whatever, may have been entirely unsuspected until the patient is annoyed or perhaps alarmed by a nosebleed, hæmoptysis, hæmatemesis, hæmaturia, deafness, or disturbance of vision, and consults the physician, who recognizes the nephritis as the cause of these bleedings.

The *skin* shows no characteristic features. Frequently it is dry and may occasionally be the seat of various lesions, eczema of various types being the one most frequently encountered. Itching is sometimes complained of, and is to be regarded as of toxic origin, comparable to the pruritus of diabetes, jaundice, and Basedow's disease. At times the itching may be noted early, and it may be so severe as to reach the dignity of a serious complication, especially because of its interfering with sleep.

Pigmentation in nephritis, other than the sallow, cachectic hue already described, is relatively rare. Reference has already been made to the occasional appearance of petechiæ and ecchymoses in those patients in whom the hemorrhagic tendency leads to purpuric manifestations. Deposits of urea on the skin have been from time to time reported. This condition is certainly rare, even when renal insufficiency is extreme and uræmia at its height. "It may happen that the skin of the face, of the neck, and upper parts of the chest, and in males, too, especially the hair of the beard, becomes covered with innumerable crystals of urea. The urea is excreted in the sweat of approaching death, and crystallizes upon the skin after evaporation of the water. In one case seen by the writer the entire full beard of a patient, who lay in a state of coma, covered with tufts of such needle-like crystals; his beard looked as if it had been white-frosted, and as I came into the ward I thought the barber must have left him after soaping his face to shave him. In another instance, two days before death, I saw the face and the skin of the trunk covered with crystals of urea" (Bartels[1]).

A sensitiveness to cold (cryæsthesia) is regarded by some as unusually

[1] *Ziemssen's Encyclopedia*, American translation, xv, 430.

common in nephritis. So also the paræsthesias described as tingling, numbness, especially in the fingers and toes ("dead fingers," *doigt mort*), are often present in this disease. They are not, however, peculiar to it, being seen in other anæmic, cachectic states, and as is well known, being very common in pernicious anæmia and diabetes, in which anatomical nervous lesions are found to explain them.

The *rarity of œdema* in chronic interstitial nephritis has been already mentioned. This should not be understood as meaning that such œdema never occurs. The œdema of cardiac incompetence very often appears late in the disease. A slight puffiness of the eyelids or a little pitting of the skin on pressure about the malleoli is sometimes seen. And it is to be remembered that not all cases fit accurately into our somewhat artificially made classes. Not infrequently one sees a case that is clearly of the type of the chronic interstitial variety in all respects save perhaps a little œdema, yet there is this one indication that the pathological process in the kidney is, after all, a diffuse one. Œdema in contracted kidney may be due also to an acute or subacute exacerbation of the nephritis, *i. e.*, we have a chronic nephritis plus an acute process.

The *nervous symptoms* in chronic interstitial nephritis are in number legion, in their variety protean. Nearly all of them may, however, be regarded as toxic or hemorrhagic. The chronic degenerative and sclerotic lesions of the central nervous system are seen with comparative rarity, and acute inflammatory processes are due to complications.

The symptoms of *toxæmia* may show themselves in mild manner and for months or years, their manifestations being so slight and the increase in severity so gradual that the patient is hardly aware of the fact that he is in ill-health. Yet on analysis of the testimony of the patient and his observing friends it will often be found that for some time there have been noted an easy mental fatigue, a lack of power of concentration and of the former quick grasp of business affairs; sleep may be poor, or the patient is drowsy during the day. He wakes in the morning with a headache, is annoyed at times by a full feeling in the head or by transient dizziness. He becomes easily discouraged, has fits of the "blues," is more subject than is natural for him to spells of despondency. He grows irritable or morose. He tries dieting, takes a short vacation, uses laxatives and tonics, but obtains only temporary relief. It is only when he consults his physician that the true underlying renal cause for these symptoms is discovered. During the further course of the disease these symptoms may become more pronounced. Conditions of semistupor may be present for days, or there may be periods of excitement. While delirium and mania are oftener seen late in the disease, they occasionally break forth rather abruptly when the patient seems to be doing well, or possibly before the individual regards himself as a patient, before he has noted symptoms of gravity sufficient to induce him to consult a physician. Delusional insanity (*folie Brightique*) is occasionally met with, and the delusions, *e. g.*, of persecution, may be so extreme as to make it necessary to place the patient under restraint in an asylum. True melancholia is not encountered so often.

Many nephritics are great sufferers from *pain*. Pain in the back, popularly regarded as so frequently an indication of Bright's disease, is a very rare complaint. That a disease of the kidney can exist for a long time without causing pain over the region of the kidney is often the occasion of great

surprise to the layman. A rare occurrence is colicky pain in the renal region often radiating along the ureter, as in true calculous renal colic, and accompanied by hemorrhage, often profuse. Some cases have been described as essential renal hemorrhages from supposedly normal kidneys, but in others that have been operated upon or otherwise carefully studied, definite nephritic lesions have been proven. Blood clots passing down the ureter explain the pain in some cases. In others, and perhaps the greater number, the explanation is probably that of Israel and of Askanazy, that both the hemorrhage and the colicky pain are to be ascribed to paroxysmal congestion.

Neuralgias in the peripheral nerves may be the cause of pain, and peripheral neuritis is sometimes clearly demonstrable in these cases. But the most frequent form of nephritic pain is headache. It may come on insidiously, but the attacks of pain grow more severe and more frequent. It may be like migraine in its periodicity and its hemicranial limitation. No one kind of headache is characteristic of nephritis. It is variously described by patients both as to its location and its character. And writers refer to it differently, one saying it is generally occipital, or occipitofrontal, another coronal, another a throbbing headache aggravated by change of position. The *resemblance to cerebral tumor* in some instances is worth noting. The severe headache, accompanied as it often is with nausea, vomiting, dizziness, and perhaps some mental disturbance, may resemble the symptom complex of tumor of the brain, and when an inflamed and swollen optic disk is discovered, one might readily be deceived were the examination to go no farther.

It is often remarkable for how long a person will let a headache, even one of severity, go unheeded, while he would become alarmed over a pain in the back or over the region of the heart, fearing kidney or heart disease. Headache is such an ordinary, every-day occurrence that familiarity breeds contempt concerning it. The physician should let no persistent headache pass without a careful urinalysis, and should be especially suspicious of those headaches that make their first appearance at about the age of forty years, and suspicious also of a sick headache that, instead of growing better at about the age of forty-five years, continues with its old severity or even grows worse. The headaches of nephritis go far to explain some of the loss of sleep and irritability of temper noticed in some of these sufferers.

The paræsthetic sensations sometimes described have been mentioned in discussing the cutaneous manifestations—the dead fingers, the itching, cryæsthesia either on contact or without, a sense of an "electric shock" especially just as one is falling off to sleep. *Cramps in the muscles*, especially those of the calf of the leg, are often annoying. At times the frequent recurrence of these cramps and their painful character seriously interfere with sleep, for they are prone to appear at night.

The so-called uræmic *palsies* must be mentioned. These are pareses or paralyses that may resemble, in their sudden onset and involvement of one-half the body, a hemiplegia from hemorrhage. But the paralysis is more commonly short-lived, lasting perhaps but a few seconds, minutes, or hours, and it usually is much more limited than to one-half the body, involving only an arm, a leg, or one side of the face. Transient aphasia is noted occasionally, or a deafness, or diplopia due to paralysis of some of the ocular muscles. These are comparable to the sudden, transient blindness, the uræmic amaurosis, and like it are central in origin, due to local cerebral œdema,

or local concentration of the action of toxins on some motor centre, with temporary loss of function of a limited area of the brain. Minute hemorrhages or areas of acute softening may possibly explain some of these cases.

Why *uræmic convulsions* sometimes occur in such a sudden manner, unheralded by warning symptoms, is not clear. Apparently there is a cumulative action of the toxin, as is seen in the case of certain drugs; similar cumulative action is seen in lead poisoning, when though the metal has been exerting its deleterious influence for a long time, the colic or the wrist-drop may come abruptly. Usually premonition of trouble is given by severe headache, vertigo, nausea, dimness of vision, epigastric pain, and perhaps a rise in blood pressure. The patellar reflex is generally exaggerated under these circumstances.[1]

When a convulsion occurs there is seldom any aura as in epilepsy, nor is there the cry so often heard in that disease. The eyes roll upward and usually to one side, the pupils dilate, and for a moment the patient seems gazing with a fixed stare into distance. Then a jerking of the angles of the mouth is seen, the head draws to one side, the muscles of the face and neck become clonically convulsed, the fingers and arms are flexed and likewise convulsed, and soon the entire musculature of the body is in irregular, jerky, violent motions. The face becomes livid or purple; foamy saliva issues from the mouth, and it may be streaked with blood that comes from a bitten tongue. The pulse grows rapid and weak, perhaps irregular, during the seizure. There may be involuntary evacuation of urine and fæces. A few seconds or minutes are consumed by the attack, which ends with a quieting of the muscular spasm, a deep-drawn inspiration, and a rather prompt recovery of consciousness. If, however, the patient has been in a stupor or coma preceding the convulsion, or if the attacks are frequently repeated, sleep, stupor, or deep coma will follow. Usually the patient is somewhat dazed for a time, and knows little more of the attack than that "something has happened." Where attacks are repeated at short intervals the temperature often rises and pre-agonal temperatures of 105° F. or over are not unusual. The pulse, too, after frequently repeated convulsions, becomes gradually more rapid and weak.

Convulsive seizures, in which the cerebral irritation is localized and the spasms of the Jacksonian type, are sometimes seen. Often slight jerkings or twitching of the muscles may be noticed, and may be the cause of considerable annoyance to the patient, who tries to keep the muscles still. Nystagmus, local tremor, local tonic muscular contractions are sometimes apparently due to this same local cerebral irritation, the resulting symptoms being not unlike those of brain tumor.

Coma may be acute and not preceded by convulsions, or even by symptoms suggestive of the extreme gravity of the uræmia. Death may occur in coma without convulsive seizures. Oftener coma is preceded by convulsions or by the long train of symptoms that make up the dismal picture of chronic uræmia, months or years of malaise, loss of strength, dyspepsia, headache, recurrent vomiting, *fetor ex ore*, insomnia, dyspnœa, epistaxis, polyuria, mental depression, the gradual cutting-off of one business care after another, semi-invalidism, confinement to the house, then to the chair, and finally to the bed. Coma coming on under these circumstances is usually fatal.

[1] Lion, *Zeit. f. klin. Med.*, l, 257, and Stevens, *British Medical Journal*, 1904, ii.

The *special sense organs* may show anatomical changes or disturbances of function, none of which, however, may be called really characteristic except those of the eye. Taste is at times perverted, but seldom more so than in other severe intoxications. A loathing for food, a coated tongue, a fœtid breath, are often coupled with the statement on the part of the patient that "food does not taste good" or things taste wrong. Complaints are occasionally heard of inability to smell or of disagreeable odors when none are about.

Hearing is usually good. But there is often a ringing in the ears that is out of all proportion to the degree of anæmia present, and that is to be viewed as toxic. Deafness, partial and transitory, may occur, comparable to the amaurosis and uræmic palsies, and apparently due to disturbance of the auditory centres, as by œdema, toxic overirritation, or possibly minute hemorrhagic or inflammatory processes. Hemorrhage into the middle or inner ear is occasionally the cause of deafness, and a vertigo resembling that of Ménière's disease has been described (*vertigo Brightique*).

The *ocular* manifestations of chronic interstitial nephritis are common. For this reason and because of certain features that are peculiar to this disease, they deserve to be considered from the point of view of diagnosis as of the first rank. Often, indeed, the diagnosis of this form of renal disease is first made by the oculist, or the crucial and convincing test is the finding on examination of the eye. While the retinal changes are the most characteristic, other subjective and objective symptoms are worthy of note.

The amaurosis, of which mention has already been made, comes on, as a rule, suddenly, may be complete or partial, is bilateral and commonly transitory, lasting but a few minutes, or at most a few hours. As has already been stated, this is one of the uræmic palsies, and of central origin. Retinal examination in these cases shows nothing to explain the blindness.

Diplopia due to uræmic palsy of some of the ocular muscles is occasionally seen. So, too, are conjunctival and palpebral hemorrhage. While œdema is not at all characteristic of this particular form of nephritis, the watery eye, the "Bright's eye," so called, may be observed. Exophthalmic prominence of the eyeball—unilateral or bilateral—has been noted several times when no other evidence of Basedow's disease was present. Insufficiency of the external muscles of the eye, emaciation of structures about the eye, undue fulness of the retrobulbar vessels, or rarely a hemorrhage in the orbit help to explain this rather odd occurrence.

Retinal changes may produce no disturbance of vision that attracts the attention of the patient, and are only discovered as the result of routine examination, which examination, it is needless to say, should always include the use of the ophthalmoscope. One is often astonished to note the extensive retinal alterations present in the eyes of those who make no complaint of visual disturbances. On the other hand, the lesion of the retina may be manifest by marked and sometimes early symptoms. It is particularly in patients of this class that the diagnosis of nephritis is made by the oculist, who is consulted before the physician. In rare instances these ocular lesions have been found before the urinary evidences of a chronic nephritis can be made out. The symptoms will naturally vary much with the extent to which the retina is involved, and especially with the damage wrought in the macular region. Dimness of vision, blurring of the outlines of objects seen, an appearance of a mist or veil before the eyes are often described.

Blind spots may cause the patient unconsciously to turn the head to one side or the other, so that the light from the object looked at may strike the healthy, undamaged part of the retina, or he may be conscious of his ability to see much more clearly objects located in one position than in another, realizing that he has some defect in eyesight. This loss of perfect vision may be much more manifest when one eye is closed, the remaining open eye being the one more seriously involved, but its visual loss being unperceived when the comparatively healthy eye is working. The changes in the retina of Bright's disease may be found in other forms than the chronic interstitial nephritis. They are, however, much rarer in either the acute or chronic parenchymatous form, and in amyloid kidney unassociated with chronic indurative processes they are probably not found. With the kidney of pregnancy, especially when it is of rather long standing, they are not uncommon. Retinal hemorrhages, too, are found in the eyes of those with general arteriosclerosis, where the lesion is to be viewed as but one of the consequences of the general vascular disease and not as depending primarily on the renal change.

Many retinal changes have been described in connection with Bright's disease, some of which are quite rare and in a measure accidental. For these changes and for minuter details concerning the retina in nephritis, works on ophthalmology should be consulted. But the general practitioner, both because of the great aid that it often gives in the way of diagnosis, as well as in prognosis, should be able to recognize certain coarse retinal lesions as characteristic of nephritis. He will often be in doubt as to the nature of what he sees, when he will ask help of the expert ophthalmologist; or with ocular symptoms inexplicable by any of his own findings he will likewise consult the specialist for help.

The commoner changes in the retina of Bright's disease are whitish or yellowish patches, hemorrhages, diffuse retinal opacity from œdema, optic papillitis, diffused retinitis, atrophic changes consecutive to inflammation. Of these six changes enumerated by Gowers, the first three are common. Tirard would add to the last three, the more uncommon, the occasional occurrence of extensive retinal detachment, which, of course, seriously impairs vision. Rosenstein also cites this as sometimes seen.

No appearance is more strikingly peculiar than the yellowish or white spots that are seen about the disk and macula or scattered more widely throughout the retina. The spots may be but minute, glistening dots, or they may be larger and represent the fusion of several smaller ones. Spots as large as the disk may be seen; these larger ones are more apt to be located near the disk, and are thought by some to represent a more advanced stage of the degenerative process. Most characteristic is the grouping of small spots about the macula as a centre from which they radiate, fan-like, in every direction, each ray being made up of a succession of these whitish areas arranged as a broken line. The macula may appear dark red. At times the whitish areas are scattered so freely throughout the retina as to present an appearance as though one had with a fine brush spattered white enamel paint over its surface.

Hemorrhagic extravasations are often present, sometimes with and sometimes without the whitish areas. These may be minute dots, larger irregular patches, or lines and streaks of blood running beside the vessel. They are sometimes "flame-shaped." In color the blood may be bright red, darker,

or a whitish atrophic patch may mark the site of the absorption of the small clot. These hemorrhages are perhaps more apt to occur in cases of renal disease associated with marked arteriosclerosis, yet they are often found in cases of primary chronic interstitial nephritis where the sclerosis of the vessels may be insignificant. The retinal hemorrhages of chronic nephritis are commonly bilateral, as, indeed, is true of the other retinal changes described.

Any extensive unilateral hemorrhage in one with arteriosclerosis is more apt to depend primarily upon the sclerosis than upon the renal mischief. The sclerotic vessels of the retina are often bright, almost metallic or wire-like in appearance. The central light streak is very distinct and sharp, while the whole surface of the vessels is somewhat lighter than usual. The reflex of the arteries is exceptionally bright.[1] In some of these cases the veins are distended, especially distally to the point where an artery crosses such a vein. These tortuous and distended veins are seen also in the cases where there is a neuritis or a neuroretinitis. Here the disk is usually slightly reddened and a trifle swollen, or it is greatly swollen and its outlines and all its details obscured. The arteries are small. Grayish and whitish streaks run out from the disk, the contour of the vessels often being lost at this point. Hemorrhages near the vessels, close to or at a distance from the disk, may be seen. The retina may appear slightly cloudy. The loss of transparency and the slight opacity of the retina are often extremely difficult to recognize.

The essential nature of each of these retinal lesions is not entirely clear, although they seem dependent on the degenerative changes in the vessels, the high blood pressure, and perhaps upon the toxæmic condition, or even in a measure upon the general malnutrition of the advanced nephritic. They are generally regarded as degenerative rather than inflammatory. The narrow, hyaline, and sclerotic arteries so often seen in the retina, the vein distended peripherally by the pressure of the stiff artery that crosses it, may help explain nutritional disturbances and degenerative results. And similarly the altered vessel with the high blood pressure makes the occurrence of hemorrhages easily understood, although the influence of toxæmia, with resulting tendency to hæmolysis or local destructive action of toxins, in the production of the whitish areas and the hemorrhages is not to be overlooked.

These changes in the retina, often collectively referred to as *albuminuric retinitis*, are seen far oftener in advanced cases when vascular degenerative, perhaps markedly sclerotic, changes are pronounced, blood pressure high, and toxæmia clearly manifest. They are rightly looked upon as of bad prognostic import. The observation that patients seldom live more than two years from the time albuminuric retinitis is discovered has been abundantly confirmed. More systematic ophthalmoscopic examination of the milder cases of nephritis and examination earlier in the course of this disease will probably reveal instances in which this retinal condition lasts longer. In fact, reports are made showing exceptions to this rule, and even Rosenstein, who cites as very remarkable the reports by Liebreich and von Graefe of instances of recovery from albuminuric retinitis, refers to a case of his own in which a woman did not die of her chronic nephritis until after seven years from the discovery of the degenerative retinitis.

Of their great help in the way of diagnosis there can be no question.

[1] Gunn, *Transactions of the Ophthalmological Society*, 1892, vol xii.

The albuminuric retinitis is often detected by the ophthalmologist, and leads to the recognition of the underlying nephritis. In office examinations, at times, the patient cannot furnish a specimen of urine, or the particular single specimen is free from albumin; the clue to the diagnosis may, under these circumstances, be given by the retina. In cases of coma it is sometimes of immense help in diagnosis to find the characteristic retinal changes. In acute exacerbations of a chronic nephritis whose existence may have been unsuspected, the finding of albuminuric retinitis speaks for the existence of a process of longer standing than the urine and œdema might suggest, for these retinal changes, as already stated, are relatively uncommon in the acute forms of nephritis.

It must not be forgotten, on the other hand, that retinal appearances much like those seen in Bright's disease may be seen under other circumstances. The swollen disk of brain tumor, meningitis, and other intracranial lesions, as well as of severe anæmias, lead poisoning, etc., must be kept in mind. Nor must it be overlooked that hemorrhages may often be seen with the ophthalmoscope in pernicious anæmia, leukæmia, ulcerative endocarditis, sepsis, the so-called hemorrhagic or purpuric diseases, etc. And even whitish flecks are seen in diabetes and the kidney of pregnancy.

Care must therefore be exercised in the interpretation of the retinal condition, and while some of the retinal appearances are almost pathognomonic, the safer way is to reach a conclusion as to the existence of nephritis only after a comparison with the other subjective and objective findings, *i. e.*, to make albuminuric retinitis, like albuminuria and cardiac hypertrophy, take its place as a confirmatory sign in the symptom complex rather than as an essentially pathognomonic sign.

Complications.—In the strictest sense, cardiac incompetence and dilatation may be regarded as the natural sequences of chronic interstitial nephritis, and, therefore, not to be viewed as complications. But the failing heart so often dominates the picture, and so modifies the course of the disease as to justify its being looked upon as a complication. True valvular disease from preceding endocarditis or sclerotic process is, of course, a complication in the narrower sense of the term. In its effects upon the nephritis it is practically identical with the secondary dilatation just referred to, and may be discussed along with that topic. The basis of the cardiac weakness is the exhaustion of the myocardium, which in many instances shows anatomical evidence of fibrous myocarditis, largely the result of nutritional disturbances due to sclerosed coronary vessels, with resulting anæmic necrosis and replacement of the destroyed parenchymatous tissue by that of a fibrous nature.

Whether or not such gross or microscopic change in the heart muscle can be made out, the heart, although enlarged, finally from overwork shows signs of weakness. Dyspnœa is marked upon even slight exertion; it may be of the nocturnal, asthmatic type already described. There is an annoying cough, and cyanosis becomes manifest. The ankles and legs show œdema, the liver is passively congested and can be felt below the costal arch, tender upon pressure, or causing, even when no pressure is made, epigastric and hypochondriac sense of weight or even pain. Gastro-intestinal disturbances are more marked because of congestion of the vessels in the walls of the stomach and bowels. Ascites may develop. The kidneys show the result of lowered blood pressure and general passive congestion, the urine becoming scantier, of higher specific gravity, and containing more albumin and casts.

In a word, the picture is cardiac rather than renal, the picture of the later stages of valvular disease, and an examination of the patient at this time, if the previous nephritic condition be unknown, may easily lead one to regard the disease as primarily of the heart. For the heart is enlarged, the apex to the left and downward, its impulse perhaps the typical diffuse, feeble, wavy impulse of dilatation, although much of the old snap and force to the first sound is often left. A systolic murmur is heard, due to the relative mitral leak, and the pulmonic closure may be sharp, the aortic sound also sharp, although weaker than before the cardiac failure. The heart's action may be irregular and the pulse small. Gallop rhythm is frequently to be noted. Such a complication as cardiac incompetence, it is needless to say, is serious, with its possibilities of general passive congestion, hydrothorax, extreme ascites, thrombosis, or complete failure of the heart. And the danger from severe uræmic manifestations is increased, as the already diseased kidneys are now seriously congested and renal insufficiency is more marked. Unless rest, dietetic and drug treatment can restore the tone of the heart muscle, the cardiac complication is liable to be the immediate cause of death.

Reference has just been made to congestion of the kidney superimposed on a chronic nephritis. Another complication in the kidney may be an acute inflammatory process engrafted on the chronic. Sometimes a cause for such exacerbation can be discovered in an exposure to cold or damp, overexertion, an acute infection like pneumonia, acute bronchitis, or an angina, but often no explanatory cause can be assigned. But the urine becomes scantier and of higher specific gravity, the albumin is increased in amount, and casts are abundant. Blood may be present in the urine. Œdema of the eyelids, face, scrotum, or sacral region may appear. And as in an acute nephritis, there may be anorexia, nausea, headache, dizziness, etc. Such exacerbations are not uncommon, and easily pass for acute nephritis unless the previous existence of the underlying chronic trouble is known. Such acute exacerbations may recur from time to time in the course of chronic interstitial nephritis, and death is not infrequently due to this cause.

Hemorrhage has been referred to as a common symptom of this form of nephritis. Under certain circumstances the hemorrhage is of such a character as perceptibly to modify the course of the nephritis or even seriously to threaten life. Hemorrhage from the kidney may be of this nature. Epistaxis, as already stated, has occasionally proven fatal. The most common serious hemorrhage, however, is cerebral. This is usually in or near the internal capsule, is like the ordinary "stroke of apoplexy," and needs no further word of description. In the case of an otherwise unexplained cerebral hemorrhage one should always think of the possibility of an underlying chronic nephritis. And it is well also, in giving a probable outlook in a case of this form of kidney disease, especially when blood pressure is high and peripheral vessels sclerotic, to remember the possibility of the occurrence of this all too frequent and often fatal vascular accident.

Alcoholism, syphilis, preceding infections, or general arteriosclerosis help to explain the occasional accompanying hepatic cirrhosis. Stewart found this in 15 per cent. of his cases.

Catarrhal inflammation of mucous membranes is a very frequent, in fact almost constant, occurrence. At times these inflammations are severe, and the bronchitis, gastritis, or enteritis may be regarded as complicating conditions. These inflammations may be looked upon as in part congestive, as in

the bronchi, stomach, or bowel, with a failing heart; in part they are uræmic; in part, perhaps, toxic, in the sense that the mucous membrane is trying vicariously to eliminate poisons that should be eliminated through the kidney and is irritated by such poisons; in part microbic, infectious organisms more readily attacking the mucous membrane of larynx, bronchi, or intestine, when the conditions of congestion and irritation from toxins and general toxæmia are present, as is the case in Bright's disease. The uræmic ulcer of the intestine, a possible explanation for persistent diarrhœa, or even severe intestinal hemorrhage, has already been mentioned.

The serous membranes seem peculiarly vulnerable during the course of nephritis. Peritonitis in the writer's experience has been extremely rare, although mentioned by nearly all authorities as relatively frequent. Pleuritis and pericarditis are much more common. Some of the cases described as pleurisy and pericarditis are probably instances of hydrothorax or hydropericardium, the fluid being a transudate rather than a true inflammatory exudate. But pleurisy and pericarditis due to infectious germs often occur. These infections are frequently mild, perhaps due to not very virulent organisms, and the resulting fever and pain may be slight. In fact, both these complications, particularly the pericarditis, are apt to be insidious and to remain latent, and they are readily overlooked. Some of the most embarrassing surprises of the autopsy table are the disclosures of pleurisy and pericarditis unsuspected during life. The signs of pericarditis are notorious for their rapid change in character from day to day. Tirard thinks renal pericarditis shows this peculiarity to an unusual degree.

The lowered vitality of the nephritic makes him particularly liable to infectious diseases. Pneumonia is not infrequent (Stewart, 7 per cent. of cases). The mortality, however, is not so much higher as one might expect, except when the pneumonia—often here a bronchopneumonia—occurs as a complication in the later stages, when cardiac and renal incompetency have become marked and when death seems not far distant even without the complication. Other infections, such as erysipelas, angina, rheumatism, septicæmia, may also occur.

Diagnosis.—Attention may here be called to the not infrequent disparity between clinical diagnosis and pathological findings. All writers make reference to the occasional failure of agreement of the clinical and pathological diagnoses. Stewart, for example, describes a case in which the postmortem lesion was sufficiently distinct, yet there had been no albumin or dropsy during life, and no suspicion of nephritis. Such cases are not rare. Cabot[1] and Emerson[2] have lately forcibly emphasized this point, making one feel really skeptical regarding our ability to make a correct intra vitam diagnosis of nephritis. Some of these errors are due to attempts to make a diagnosis with insufficient anamnesis, so that a case is regarded by the clinician as acute, while the pathologist finds it to be chronic, or vice versa. And some are merely instances of an unwise enthusiasm that induces one to attempt to make a too refined anatomical diagnosis, perhaps an impossibility in the particular case, and that often leads one to forget the fact that the mere ability to predict the anatomical lesion is not after all the highest aim of the clinician, the detection of etiology and perverted function, together with means of relieving the same, being of really greater importance.

[1] *Journal of the American Medical Association*, March 18, 1905.
[2] *Ibid.*, January 6, 1906.

Some of these discrepancies are, of course, simply errors or blunders. Again, hasty examinations, examinations of single specimens of urine instead of the twenty-four hours' urine, failure to study the heart and blood pressure, or to examine the eye grounds, permit a case that should be easily diagnosed to go to the autopsy table with no suspicion of renal disease, while the pathologist finds marked changes; or that the arteriosclerotic kidney is frequently present, although a non-albuminous urine is passed, is often overlooked; or the pathologist classes as chronic nephritis what really should be regarded as an arteriosclerotic, atrophic kidney. Again, a small area in the kidney, perhaps a small infarcted patch, may be causing a slight albuminuria and cylindruria and lead to the clinical diagnosis of nephritis, overlooked postmortem, and the kidney passed as normal. Albuminuria from a congested kidney, from an altered blood state, or from febrile conditions where there is but an acute parenchymatous degeneration of the kidney, may lead to a mistaken diagnosis of nephritis. Carelessness may also lead to misinterpretation of albuminuria due to pus or blood in the urine from some cause other than nephritis. If due care and diligence be exercised by both clinician and pathologist, and if due recognition be given the arteriosclerotic kidney, the number of discrepancies will be very small indeed. Yet there must always be some failures on the part of clinician and pathologist. The latter may easily overlook changes in an organ whose macroscopic appearance may be that of health, while the microscope reveals definite changes of nephritis, or even with the microscope the change may be overlooked, as the particular portion of the kidney studied may be normal, the diseased patch escaping examination. Or, again, a portion of the kidney evidently diseased may represent a scarred, healed area whose function is nil, and which would give no evidence of its existence during life by albumin or casts. The exact point in the nephritic process at which albuminuria and cylindruria begin is not known. The anatomist may find evidence of pathological, even acute inflammatory, change in the kidney, although no urinary or other evidence of disease has been present, or the clinical evidences of the acute nephritis may have passed away, and there still be left definite anatomical lesions. We must remember, too, that all are agreed that nephritis, both acute and chronic, may exist without albuminuria.

This is not an attempt to argue the incorrectness of the views of those who point out the glaring inconsistencies between our clinical and necropsy findings, for there is no doubt that such discrepancies are met with, and they illustrate but too well our present limitations in diagnosis and our still imperfect knowledge of the relation between anatomical renal change and malperformance of renal function. But while some such mistakes are inevitable until a more nearly perfect knowledge of the physiology of the kidney is known, and the means of detecting perversions of the same and of recognizing the basic lesion that exists are more exact, we still believe that greater care and practical application of the knowledge already known by both clinician and pathologist will greatly reduce the number of such so-called mistakes in diagnosis. And while it is no defence of such errors to call attention to somewhat analogous mistakes with reference to other organs, it is perhaps some comfort to know that a careful clinician may overlook an anatomically demonstrable valvular lesion of the heart, or the pathologist may insist that there is no anatomical evidence of such defect, when the clinician knows by every sign and symptom that such a defect—functionally at least—

did exist. All of which goes to prove, as said, that our knowledge of disease is still far from exact and that Hippocrates' aphorism is still true, and that "experience is fallacious and judgment difficult."

Failure to examine with thoroughness, and not ignorance, is, as in the case of many other diseases, the commonest cause of error in diagnosis, at least the error of overlooking entirely the existence of chronic interstitial nephritis. He who carefully examines his patient will seldom miss the urinary and cardiovascular evidences of disease of the kidney. It seems trite, and it is perhaps unnecessary, to repeat what has been so often said by teacher and writer, that the physician should not wait for a direct and pointed suggestion that there is renal disease before examining the urine. Without complaint on the part of the patient of pain in the back or change in the frequency of urination, or in the amount or naked-eye appearances of the urine, the urine in every new patient should be investigated. And so also the heart should be subjected to a careful physical examination, even although dyspnœa, palpitation, or precordial distress may be lacking. Most exasperating and sometimes serious blunders may thus be avoided. This sin of omission is the more readily committed by the family doctor, who is familiar with his patient, and who has perhaps in previous years examined the urine and the heart and found them normal, and who, therefore, does not now, when his patient comes to him with some apparently trifling ailment—it may be headache, dizziness, anorexia, general weakness—think it necessary to reëxamine, forgetting that marked changes may have occurred in the course of the months or years that have elapsed since the last careful physical examination was made. A searching inquiry into the subjective history may give hints as to the existence of renal trouble. The passage of larger amounts of urine than formerly, the necessity of emptying the bladder frequently, and particularly the history of frequent nocturnal urination with considerable urine passed each time, are among the most suggestive facts. It may be well to repeat the caution that when there is the least suspicion of renal mischief one must not be content with negative findings in a single specimen of urine, but must examine several specimens or the twenty-four hours' urine.

This careful examination will usually prevent the overlooking of the disease. It will also usually enable one to make an accurate diagnosis, ruling out other possibly confusing conditions. At times, however, the contracted kidney may be mistaken for some other malady, or some other disease regarded as chronic nephritis, and what is little more than a list of such possibly confusing conditions, with some of the more salient differential diagnostic features, is given here, although some of these conditions are promptly ruled out by the exercise of even elementary knowledge and carelessness might make it necessary to add many other diseases to this list.

With failing heart, the differentiation from primary *valvular*, *myocardial*, or *pericardial disease* (adhesive mediastinopericarditis) is not always easy, and at times is possible only when one has exact first-hand knowledge of the previous history, with accurate physical examination, or has the opportunity of watching the patient and seeing the effect on the urine of improvement in the condition of the heart under rest and appropriate drugs. The history of preceding rheumatic fever or chorea, of dyspnœa, cough, and palpitation; the absence of polyuria in the past; the fact that the patient's urine may have been examined some short time before and pronounced normal, or that he

was rejected for life insurance because of rapid heart or increase in size of the heart, or a murmur, but not on account of the urine, are all facts that point in the direction of primary cardiac disease. The co-existence of aortic or of stenotic mitral lesions with the mitral leak is evidence in favor of organic valvular disease, as are signs of adherent pericardium. No test is, perhaps, of as much value as the therapeutic one of putting the patient at rest, restricting the diet, and administering suitable remedies, such as digitalis, cathartics, etc. If under these circumstances the heart diminishes in size, the apical murmur becomes louder, and the sound of the pulmonic closure grows sharper and more accentuated; and if with these evidences of improvement in cardiac tone the œdema disappears, the urine increases in quantity, the albumin and casts vanish, one may be reasonably certain that primary nephritis is not the cause of the cardiac incompetency. If, on the contrary, with improvement in the cardiac condition and disappearance of dropsy the mitral murmur disappears or grows fainter, if the aortic closure takes on a sharp, ringing, accentuated character, and if the urine increases to more than the normal in amount, and retains a low specific gravity, and if casts and albumin are constant findings, one may conclude that there is primary nephritis with secondary cardiac trouble.

The urine of pure *congestion of the kidney* is apt to be much more reduced in amount, of higher specific gravity, and to contain a smaller amount of albumin and fewer casts than when the congestion is superimposed upon a previously existing chronic interstitial nephritis by the giving way of the heart. Even when congestion is added to the chronic interstitial nephritis, the amount of urine may remain normal and the specific gravity will often be below 1020 or 1018. With the pure congestion from primary heart disease, the amount of urine is often as low as 400 to 800 cc., and the specific gravity is usually 1020 to 1030. The absence of albuminuric retinitis and of typical uræmic manifestations may have some weight in influencing one toward the diagnosis of primary cardiac disease.

The difficulty of diagnosis is also great in many instances of *general arteriosclerosis* with enlarged heart and perhaps a systolic murmur at the apex and base from roughened mitral and aortic valves, and with albumin and casts in the urine. Differentiation between the primary nephritis with secondary arteriosclerotic vascular and cardiac changes may not be possible, and in a sense is not always of great practical importance. If the facts of the earlier history are obtainable, it may be shown that the thickened vessels and enlarged heart were present at a time when polyuria and albuminuria were slight and inconstant, and that they were marked long before any symptoms that could be classed as uræmic were manifest. Albuminuric retinitis will be rare, although unilateral retinal hemorrhages may occur. Angina pectoris, irregular action of the heart, perhaps the Stokes-Adams syndrome, as evidences of myocardial degeneration, are more apt to be prominent symptoms than urinary changes or uræmic manifestations.

There is seldom cause for confusion of typical cases of either acute or chronic *parenchymatous nephritis* with the chronic interstitial variety. The abrupt onset of the acute form following some infection, the frequent occurrence of general œdema, the scantiness of the urine, its higher specific gravity, the abundance of albumin, the numerous casts and the blood, stand in striking contrast to the insidious onset, absence of œdema, large amount of pale urine of low specific gravity, with but few casts, and but a small

amount of albumin. The chronic parenchymatous form with marked œdema, scanty, richly albuminous urine, with its heavy sediment largely made up of casts, epithelial cells, fat globules, and granular debris, presents a picture strikingly different from that of the disease under consideration. And in both the parenchymatous forms cardiovascular changes are less marked and albuminuric retinitis is less likely to be present.

It is not, however, an easy matter to determine in a given case whether there may not be a combination of chronic interstitial nephritis and the acute form, *i. e.*, an acute process engrafted on the chronic, a so-called *acute exacerbation* of the chronic. This condition is by no means infrequent. The urine in many respects will resemble that of acute Bright's disease; albumin and casts will be plentiful; blood may be present and the amount of urine may be less than normal. Œdema may develop. The existence of a long-standing nephritis may perhaps be suspected from the history of polyuria, thirst, and palpitation; marked enlargement of the left ventricle, sharply accentuated aortic tone, and albuminuric retinitis, also point in the same direction. Often, too, a low specific gravity, say 1013, although the other urinary findings are those of acute nephritis, will raise the question of the existence of a long-standing chronic nephritis. Rest and time may clear up the diagnosis as the acuter process disappears, leaving the case a clear one of chronic interstitial nephritis.

It has been stated on a preceding page that many cases of chronic nephritis are both pathologically and clinically of a character that must be regarded as diffuse. Our efforts to make these cases fit into the category of chronic parenchymatous or chronic interstitial nephritis are futile, and the only diagnosis that we may make and the one that is in reality scientific and justified by clinical and anatomical facts is the diagnosis of chronic nephritis or *chronic diffuse nephritis*. Such a diagnosis seems to be warranted when in a chronic nephritic there is moderate œdema, definite left ventricular hypertrophy, and increase in blood pressure, with a urine fairly rich in albumin and casts, yet of a specific gravity somewhat below normal, say 1014, and in amount varying, being at times normal or again somewhat more than normal. There may be the anæmia and cachexia of nephritis, and uræmic and retinal manifestations may or may not be present. In brief, we have the œdema, the abundant albumin and casts of chronic parenchymatous nephritis, with the cardiovascular changes, the retinitis, the uræmia, and some of the urinary findings of the chronic interstitial variety.

Secondary contracted kidney may be recognized if one has had the opportunity of watching the patient go through the stage of œdema and abundant albumin, and has seen the enlarged heart and polyuria appear, with a coincident disappearance of œdema and a lessening in the amount of albumin and the number of casts. Without such a preceding history the best one can do is to consider the case as one of chronic nephritis, differing from the typical contracted kidney only in its tendency to have a larger percentage of albumin than normal, the amount of urine being not as great as in chronic interstitial nephritis and the casts more abundant and darker (Bartels). Some œdema may still be present.

Pure *amyloid kidney* is relatively rare nowadays. It may be recognized by the existence of some operating cause, such as tuberculosis—particularly chronic excavating pulmonary tuberculosis when associated with tuberculosis of the intestine—chronic suppurative processes, as in the bones or in the

pleural cavity, or syphilis in its later stages. The anæmia and cachexia of amyloid, the dropsy, the enlarged hard liver and spleen, and the frequent diarrhœa from amyloid of the intestine, lend color to this diagnosis. The urine is apt to vary from day to day both in amount and in its content in albumin and casts. In general it is increased in amount, its specific gravity low, and the amount of albumin considerable. Serum-globulin is present in larger proportion than in ordinary nephritis (Senator). Cardiac hypertrophy, albuminuric retinitis, and uræmia are not associated with pure amyloid kidney. In some instances postmortem examination has shown amyloid degeneration in the kidney where a chronic nephritis is also present and where during life there has been no thought of amyloid unless the existence of tuberculosis, syphilis or suppuration, or an enlarged spleen or liver has aroused suspicion of possible visceral amyloid change.

The stage of *convalescence* from an acute nephritis may prove quite confusing. Here the urine is often increased in amount, of low specific gravity, and the previously large amount of albumin is represented by a small amount or a mere trace that may persist for many weeks, as may also a mild cylindruria. The preceding history is, when obtainable, of great assistance in the diagnosis. The absence of high blood pressure and of enlarged left ventricle, and the tendency for all the urinary abnormalities gradually to disappear and for the urine to approach the normal will speak for the absence of the chronic interstitial process.

The so-called *physiological albuminuria* may be mistaken for chronic interstitial nephritis, largely because of the absence of œdema and the fact that the amount of albumin is usually slight and inconstant. The absence of cardiovascular changes, the rarity of casts, the fact that polyuria is not noted, should arouse suspicion when this condition is found in the young, that the albuminuria may not be due to an incipient chronic process. Plenty of time must be taken for a thorough study of such a case to determine as to the periodicity of the albuminuria and the influence upon it of diet, position, and exercise. The writer agrees with Krehl when he states his belief in the existence of a physiological albuminuria—using the poorly applied term physiological to mean that there is no known anatomical, at least inflammatory, change in the kidney—and that complete *restitutio ad integrum* occurs. The amount of albumin in these cases may be considerable. S. West[1] regards functional albuminuria as never in the strict sense physiological, and believes that many such patients, although at the time apparently healthy, later develop signs of disease. Senator's caution is wise when he advises one to view every supposed case of physiological albuminuria as a possible beginning chronic nephritis, and to regard an albuminuria as physiological only when it is transitory, when the amount of albumin is small, present in one who has not reached adult life, and when it appears only after what may be regarded as a physiological exciting cause, such as a heavy meal, physical overexertion, cold bathing, etc. This conservative position of Senator is surely the safe one, and will lead the physician to take sufficient time to study his case thoroughly before committing himself to the diagnosis of physiological albuminuria.

Albumin due to the presence of *blood or pus* in the urine ought not ordinarily to mislead one to a diagnosis of nephritis. The chemical and micro-

[1] *Lancet*, London, 1904, i, 143.

scopic proof of the presence of these pathological substances, the direct variation in the amount of albumin with the variation in the amount of blood or pus, the fact that filtering them out removes all or the greater part of the albumin, the absence of casts and of cardiovascular changes and uræmia, together with the presence of some cause for the hæmaturia or pyuria as stone or tuberculosis in the kidney or bladder, pyelitis, cystitis, etc., would induce one to recognize the albuminuria as the so-called spurious rather than true and nephritic. But combinations of the two conditions may be met with, as when a nephritic is a sufferer from calculous or tuberculous pyelitis; or the case may be one of ascending pyelonephritis, the so-called consecutive nephritis. Under these circumstances filtration and removal of the pus does not by any means remove the albumin; casts are found, and the blood pressure, the retinal findings, and uræmic manifestations may give evidence of the existence of a true nephritis. A case of interest in this connection has but recently been under the writer's care. A man, aged about fifty years, had been treated for some five years for kidney trouble, the physicians in each instance carefully examining the urine. He had been told of the presence of pus and albumin. He had every evidence of chronic nephritis with induration, the left ventricle was enlarged, the aortic closure ringing, the blood pressure 200 mm.; there was marked albuminuric retinitis. Headaches had recently been severe and vomiting frequent; there was moderate secondary anæmia and malnutrition. Nocturnal asthmatic attacks interfered with sleep. The odor of the breath was decidedly urinous. Œdema of the legs and puffiness of the eyelids had been noted at times, and with one attack of cardiac incompetency œdema was very pronounced in the lower part of the body. The urine was generally abundant, averaging 1012, and always albuminous. The interesting feature was the constant absence of casts and the uniform presence of pus in varying amounts, with enormous numbers of bacteria. The reaction of the urine had been at times slightly alkaline, at others neutral or acid. There was, to judge from some slight local pain and tenderness on pressure, a left-sided pyelitis of unknown cause. The absence of casts—at least twenty careful searches were made—with such unmistakable evidence of chronic nephritis seems to be explained by the presence of the countless bacteria that promptly destroy (digest?) the delicate casts as they enter the infected pelvis of the kidney and the bladder.

The thirst, polyuria, and emaciation of contracted kidney may lead one to suspect *diabetes mellitus*. The examination for sugar, with negative result, and the finding of albumin and casts make the diagnosis plain. A low specific gravity, however, should not lead one too promptly to exclude saccharine diabetes, for when a diabetic has been drinking large amounts of water, as is sometimes done for supposed curative effect, the specific gravity of the urine, even although sugar-containing, may be below normal.[1] Again chronic interstitial nephritis may develop during the course of diabetes. When this takes place, not only are there cardiovascular evidences of this occurrence, albuminuria and cylindruria, but the specific gravity of the urine is lowered, perhaps even below the normal, and, strange to say, the glycosuria may disappear. This possible combination of diabetes and nephritis ought not to be forgotten, nor should the fact be overlooked that in some cases of diabetes there may be spells of freedom from glycosuria, even,

[1] Cf. Herrick, *American Journal of the Medical Sciences*, 1900, cxx.

perhaps, when no special care as to diet has been exercised, *i. e.*, the glycosuria is for some mysterious reason periodical. A similar word of caution ought to be given concerning the possible misinterpretation of urinary findings during diabetic coma. Sugar is occasionally absent during such coma, and is often scanty. A small amount of albumin is common, and hyaline casts may be present in enormous numbers (Külz's phenomenon). Under these circumstances, were one to rely upon the presence of albumin and casts alone, the coma might easily be regarded as uræmic and the diabetic features entirely overlooked—the diacetic acid, the acetone odor, the peculiar breathing, the emaciation, the dry skin, as well as the absence of cardiovascular and œdematous "earmarks" of nephritis.

A study of the urine for a short time, with the continued absence of albumin and casts, the unusually low specific gravity, *e. g.*, 1004, and the absence of cardiac, vascular, retinal, and uræmic changes, will enable one to recognize a *diabetes insipidus*, and to distinguish it from chronic nephritis. Rarely the two conditions are combined.

The frequent urination of the man past middle years, particularly the frequent nocturnal urination, may be looked upon as due to an *enlarged prostate*, unless the examination of the prostate gland and of the urine be made. Enlarged prostate may, of course, co-exist with the nephritis. A trace of albumin or of nucleo-albumin from an accompanying cystitis may add some confusion to the differentiation, but careful analysis of symptoms and findings on physical examination will enable one to diagnose such a case correctly.

Cystic kidneys may cause albumin and high blood pressure. A careful physical examination will enable one nearly always to feel the enlarged, perhaps roughened kidneys. Rarely the enlarged cystic kidney is unilateral. Developmental faults, as hypospadias or harelip, are sometimes found at the same time.

There are, of course, numerous errors that are possible when due thoroughness is not exercised in the matter of subjective and objective examination, the mistakes being made chiefly because striking uræmic symptoms are looked upon as manifestations of independent diseases, or as due to some other cause than the underlying nephritis, which is overlooked. Such mistakes are fortunately easily avoidable, the study of the urine and of the heart being usually all that is necessary to lead to the discovery of the renal mischief. Without going into details, it may be well briefly to mention a few of these possible sources of error. Among the commoner ones is to mistake as simple *gastritis* or dyspepsia, the anorexia, distress from gas, nausea, fulness after eating, epigastric pain, vomiting, or perhaps diarrhœa that are evidences of uræmic intoxication. *Neuralgias* of various types, muscular cramps, or pruritus may have their real nephritic significance overlooked unless care is exercised. And a mistake that seems to be altogether too common is to misinterpret entirely the dyspnœic, bronchitic, and *asthmatic phenomena;* the nocturnal asthmatic seizures particularly are very characteristic, and should always lead to a urinalysis. It has been noted that chronic nephritis may resemble *tumor of the brain*, because of the severe headache, vomiting, papillitis, and such cerebral symptoms as dizziness, tinnitus, disturbances of vision, and possibly even delirium or monoplegia. The urinary and cardiovascular phenomena will put one on the right track. The simulation of *malignant disease* is not very close, yet the anæmia, emaciation, local gastric

disturbances, or perhaps hæmaturia or melæna, may lend still further color to this thought. And without the careful examination so often referred to, it is an easy matter to regard the often vague symptoms of easy tire, nervousness, anxiety, sleeplessness, poor appetite, headache, dizziness, etc., as but evidences of physical or mental overwork, or of "nervousness," or *neurasthenia*. The temporary improvement under tonics, a vacation, or a short trip away from home may be looked upon as a proof of the correctness of this view. The routine habit of making an examination of the urine in every such case would be the means of avoiding many an embarrassing blunder.

The differential diagnosis between uræmic *coma*, on the one hand, and the coma of alcohol, opium, diabetes, and such cerebral conditions as hemorrhage, embolism or thrombosis, fracture of the base, meningitis, abscess, etc., on the other, might be discussed at length, but seems unnecessary, as each case has to be studied on its own merits, and no rules or tabular scheme of differential diagnosis will be found to be available as an easy or ready reference scheme of diagnosis. The facts of the previous history, when obtainable, are often of extreme value. The urine, obtained by catheter if necessary, the high blood pressure, enlarged left ventricle, the tortuous vessels, the slight œdema, the urinous odor to the breath, and the albuminuric retinitis are all of immense help. The fact that transitory albuminuria may be present after cerebral hemorrhage, epileptic seizures, etc., should not be forgotten. And when with uræmia there is fever and delirium, the resemblance to the delirium or to the stupor and coma of typhoid or of sepsis may be striking. These cases are not so very infrequent. The writer once saw one of the best clinicians of Europe trip up on the differentiation between purulent meningitis and uræmia. Often the diagnosis of uræmic coma is to be made by exclusion. It is a pretty good rule to diagnose uræmia as the cause of coma only when one has by a careful consideration of known facts as to previous history, and after thorough examination of the patient as to temperature, pulse, cardiac condition, urine, pupils, retina, reflexes, paralysis, blood, odor of breath, etc., been able to exclude other causes. Possible combinations, such as alcoholism or cerebral hemorrhage with uræmia, must not be forgotten.

The toxic condition due to *simple anuria*, when there is suppression of urine, as from obstruction due to a calculus, or following anæsthesia, presents some differences from that toxæmia due to true uræmia, *i. e.*, nephritis. The fact of such difference has been emphasized especially by Ascoli,[1] and seems to be at times clearly made out. There is commonly less headache, less pain, less intractable vomiting, but rather a gradually increasing restlessness, anxiety, sleeplessness, and general weakness. The pulse grows weaker. There is early tendency to stupor, and little delirium, except toward the last, when the slight mental wandering finally merges into a condition of unconsciousness.

Prognosis.—Chronic interstitial nephritis is to be regarded as an incurable disease. Recovery is certainly a rare occurrence, and Senator's[2] statement that if the disease be taken early, recovery is possible, as is "indisputably shown by clinical observations and postmortem examinations," is so exceptionally true that one is justified in viewing the disease as practically incurable. This fact of the practical incurability of chronic Bright's disease

[1] *Die Uraemie.* [2] *Diseases of the Kidney*, American edition, p. 285.

has become so generally known that there has become firmly fixed in the minds of the laity and of physicians as well, the notion that the diagnosis of this form of renal disease carries with it not only incurability, but a fatal termination in the near future. This notion is fostered by the fact that hospital statistics show a frightful mortality from chronic Bright's disease, and the cases there seen by physicians or in the clinics by students, are in serious condition, and many of them clearly but a short remove from death. To get a right view of this matter of prognosis, the physician must go back to his statistics of the office consultation room, and his experience in private practice, and not let the college clinic or the ward of the charity hospital appear too prominently in the foreground. When this is done he will be surprised to find how chronic interstitial nephritis is not necessarily inconsistent with years of comfort, happiness, and usefulness, or even with ripe old age. And he learns that while it is wrong to promise a cure to the individual in whom we find the urinary and cardiac signs of that disease, it is just as wrong to hold out to him the gloomy prospect of a complete invalidism and an early demise. The dark side of the picture is too often presented to these patients, almost as a matter of routine, because the trace of albumin, a few casts, and a slightly increased blood pressure have been made out, perhaps as an accidental finding during an examination for life insurance, or as the result of a thorough overhauling in the office of the physician, who has been consulted for some trifling ailment entirely unconnected with the kidney.

The patient is entitled to know the necessity of care as to his future mode of living, and the importance of watchful and conscientious coöperation on the part of himself and his physician in the attempt to retard as much as possible the further progress of the disease; but he is also entitled to know that that progress may in the natural course of events be slow, that he is fortunate in having had detected in the urine this evidence of weakness on the part of the kidney, that it may be his salvation in leading him to regulate more carefully his habits of eating, drinking, and working, and result in a decided prolongation of life. We must make him realize that a kidney, although hopelessly anatomically diseased, may be functionally healthy and for a long time able to perform its duty. All physicians of experience have seen such patients live for many years before succumbing to the renal disease, or perhaps to some other affection. Rosenstein saw a patient in whom the chronic kidney disease had lasted thirty years. Saundby had one who was living after twenty years. Not long ago a woman, aged about forty-five years, was seen in the terminal stages of chronic interstitial nephritis, who had been under medical advice for this disease for fourteen years; how much longer the disease had lasted was not known.

There is no rule or set of rules that can be formulated by which one may decide as to the prognosis in a given case. One's experience and judgment here play important roles. The case must be considered as a whole, and attention not fixed too particularly on the amount of albumin, the number of casts, the size of the heart, the condition of the retina, etc. One must, in other words, individualize in the matter of prognosis.

While this is true, one may rightly study critically the condition of the heart and vessels, for upon cardiac integrity depends to a great extent the length of time the patient may endure the nephritis. Excessive cardiac enlargement with high blood pressure, say 175 to 200 mm. Hg., and beginning symptoms that are referable to the cardiovascular system, such as palpita-

tion, dyspnœa, etc., lead one to fear that cardiac incompetence is imminent. More marked signs of cardiac incompetence naturally make one give a rather serious outlook, as, although rest and treatment may for a time restore cardiac tone and bring about great improvement in the general condition, the rule is that such a breakdown on the part of the heart is a sign that the patient is constantly near the danger line, and that degenerative changes in the heart muscle are so advanced that it will not be possible for it to hold together much longer. Intercurrent affections and acute exacerbations naturally add to the gravity of the condition.

The so-called uræmic phenomena, when they are pronounced and persistent and when not evidently due to some acutely or temporarily acting cause, are of grave import. Such things as persistent headache, nausea and vomiting, loss of weight and strength, and the development of the cachectic appearance and signs of malnutrition are of this character. A typically "urinous" odor to the breath always seems to be associated with the severer and advanced forms of the disease. Personal experience with albuminuric retinitis tallies with the traditional fact that such a finding is indicative of an advanced kidney disease, and that death is seldom delayed more than two years. The urinary findings are rather uncertain so far as prognosis is concerned. Relative anuria is often of bad import, although it usually depends upon the condition of the heart. Toward the end albumin is apt to increase in amount. Cryoscopy of the urine gives little help in the way of prognosis, as so many circumstances whose influences cannot be estimated may modify the freezing point of the urine. The freezing point of the blood, when there is much retention of toxic material and uræmia, is threatening, is apt to be lower than normal, *e. g.*, —0.60° C., or even less than that. This, taken in conjunction with an elevation of the freezing point of the urine, *e. g.*, to —0.50° C., would be justly regarded as of bad omen.

When convulsions or coma occur, unless some acute or temporarily acting cause that may be relieved is operating to produce this result, the outlook is grave. Death in the near future is certainly the usual result in such instances.

The outlook in cases of the arteriosclerotic kidney is often grave, because of the attendant coronary sclerosis and myocardial degeneration. Yet many patients of fifty or sixty lead lives of considerable activity, although their vessels and heart show evidence of moderate sclerosis and although the trace of albumin and the few casts show that a similar condition obtains in the vessels of the kidney.

We probably do not use the sphygmomanometer as much as we might in trying to form our prognosis. Its value consists perhaps not so much in determining unusually high pressures, *e. g.*, 250 to 300 mm., in which one feels sure danger is imminent, as in noting the *change in blood pressure*. A pressure that is seen to be going steadily up from week to week or month to month, in spite of care on the part of the patient and the exercise of his best skill on the part of the physician, is naturally a cause for alarm, while one that is stationary or that under treatment is lowered to near the normal may make one feel more hopeful as to the immediate outlook. Much may be learned also by watching the blood pressure during a period of cardiac incompetence, and the future may perhaps be predicted more accurately as one sees the response in increased blood pressure under the influence of rest, digitalis, and other therapeutic measures.

The outlook in a given case often depends much on the intelligence of the patient and his willingness and ability to coöperate with the physician in carrying out treatment. It goes without saying that, other things being equal, the intelligent individual with strong will power and determination and with plenty of money has a better prospect of improvement than the ignorant, indifferent person, who is financially unable to place himself in the best possible circumstances for the preservation of his health.

The way in which death will come in a given case is very uncertain. It can seldom be predicted. Sudden coma will occasionally overwhelm one who seems to be doing nicely. Or one whose subjective symptoms are slight, whose blood pressure does not seem dangerously high, succumbs to cerebral hemorrhage. Intercurrent disease, as pneumonia, carries off a considerable proportion. A cardiac death with its dyspnœa and dropsy is reserved for a large number, while many die with uræmic intoxication. Oftenest, perhaps, the final scene is a mixture of the uræmic and cardiac, a most distressing picture, the only consolation for which is that death when it comes, seems to the friends as a kindly relief from almost intolerable suffering, and not so cruel as when it comes unexpectedly in the shape of cerebral hemorrhage, sudden coma, acute pneumonia, although to the knowing physician such sudden death, sparing the patient the weeks or months of sickroom suffering, may seem far the preferable mode.

Treatment.—How much can be accomplished in the way of warding off chronic interstitial nephritis is very uncertain. Surely not much is actually accomplished, at least consciously, because little opportunity is offered for explicitly advising as to *prophylactic measures* to be carried out for the purpose of guarding against this disease, for one is uncertain as to who is "threatened" with it. Yet a timely word of caution as to proper modes of living may be of help in this respect in the case of individuals in whose families there is a tendency to chronic Bright's disease and early arteriosclerosis. Warning may be given the worker in lead, the gouty individual, the alcoholic, and the one who is keeping pace with his more vigorous comrades in the hustle of the strenuous life and using up too rapidly his physical and nervous energy, perhaps with disastrous effects upon the kidneys and vessels. Changes in habits of living brought about by following the physician's advice in instances of this sort will occasionally undoubtedly do good in warding off this disease.

Proper treatment of an acute infection, such as scarlet fever, with especial watchfulness during convalescence, may prevent the development of acute nephritis that might possibly be the forerunner of the chronic form. Attacks of acute nephritis from whatever cause, and instances of sharp febrile albuminuria, while in no sense definitely threatening a chronic interstitial nephritis, should lead to watchfulness in the future, as they possibly indicate a special vulnerability on the part of the kidney. Recognizing the influence of chronic intoxication in the production of this form of renal disease, one should not neglect conditions that may cause such intoxications, such as repeated attacks of infectious troubles, malarial fever, oft-recurring tonsillitis, nasopharyngitis, chronic suppurative otitis, chronic bronchitis, syphilis; and one should also, for the same reason, strive to relieve chronic gastro-intestinal disorders. Cystitis and pyelitis, carrying with them not alone danger through hæmatogenic intoxication, but the danger of involvement of the kidney by direct extension, should, of course, be relieved when possible.

The greatest field for prophylactic treatment, however, is not in warding off the disease, but in guarding against its more rapid progress. Great good comes from proper advice, properly followed, in the case of the one in whom, perhaps accidentally, the evidences of incipient nephritis are found in the shape of a slightly increased blood pressure, a beginning thickening of the vessel wall, a trace of albumin, or a few casts in the urine. As Osler has somewhat paradoxically but happily said, the man of middle years in whose urine a trace of albumin is discovered is to be congratulated, for from this time on, if he be wise, he will be more careful and heed the warning thus early conveyed, modifying his excesses in the way of eating, drinking, and working.

The *active treatment* necessarily implies the removal of the operating cause, whenever possible. While this cannot always be discovered, and may not always be removable, something may at times be accomplished in the way of checking the progress of the disease by correcting disorders such as those just mentioned. Workers in lead may be instructed as to how to live, still keeping at their work, or, as is usually necessary, advised to give up this, for them, dangerous occupation. The gouty man is given instructions as to diet, the alcoholic warned of the harmful results of pursuing his habits of drinking. The man of extreme business activity is cautioned against a continuance of his excesses in this line.

All these directions are, it will be noted, along the line of preventing a continuance of the previously operating baneful influences, and to this end of sparing the kidney unnecessary work our efforts should from now on be directed. In other words, the damaged organ must be given *rest;* not absolute rest, for that is impossible, but rest compared with what it had previously been doing, and usually rest compared with what a healthy kidney might reasonably be expected to do.

Diet.—The problem presented in chronic interstitial nephritis is an entirely different one from that of acute nephritis. In this latter disease little or no food may be taken for days; temporary starvation may be of benefit; for weeks milk alone may be given. But in the chronic disease enough food must be taken to meet the demands of the body, not when it is at rest in bed, but when it is perhaps doing a fair amount of physical work; and a dietary has to be planned that, while not harmful to the kidneys, is palatable and will be tolerated for months or years. *Milk diet* alone is here an impossibility. To give enough milk to maintain the strength of an adult who is up and about means the taking daily of several quarts, and this is not always wise, because it adds to the volume of the blood and thus throws extra work on the heart, tending to increase still further the hypertrophy of the left ventricle; and, besides, it increases the demand made on the kidney in the way of eliminating water, *i. e.*, it violates one of the rules of rest, for instead of sparing the kidney all the work possible, we are asking it to do extra work. The taking of such large amounts of milk to the practical exclusion of other foods soon leads to loss of appetite and to various disturbances of the stomach and bowels, with consequent anæmia and emaciation. Occasionally only skimmed milk or buttermilk is given, either of which, robbed of its cream, that is rich in calories, is entirely insufficient properly to nourish the patient. One feels like emphasizing pretty strongly the harm done by limiting the food to milk alone, for it is no uncommon thing to see a thin, pale, weak individual, a sufferer from contracted kidney,

the accidental discovery of which malady has led to the institution of the strict milk diet treatment, who has soon tired of his food, which he takes with much loathing and upon the compulsion of a sense of duty, and who now, emaciated and weak, is a sufferer from diarrhœa, nausea, coated tongue, foul breath, and numerous other evidences of impaired digestion. That this diet of milk alone is injuring him is seen by the prompt improvement in his condition when the amount of milk is reduced and a more liberal diet allowed. And at times the strict milk diet with resulting gastro-intestinal disturbances increases albuminuria, apparently through the influence of toxins generated in the deranged alimentary canal.

The emphasis here is upon the diet restricted to milk alone. Against milk as an article of food suitable for chronic nephritis nothing can be said. It is nourishing, and, so far as can be judged, as harmless in the way of irritating the kidney as any other food; and it supplies a needed amount of liquid. It may with distinct advantage be given to such a patient, and may even be the main article of food for long periods of time. But there is still among the laity and among some physicians the notion that the moment Bright's disease is recognized the proper thing for the patient to do is to live upon milk alone, without considering what may be the variety of the disease in the given case, or what the especial needs of the particular individual. This is surely an extreme view to take, and one that may lead to harm.

Closely connected with the question as to the amount of milk to be given is the question as to what amount of *liquid* should be allowed the nephritic. There are two views concerning this. The one advocates the giving of water freely, even in excessive amounts, several quarts daily, with the object of flushing out the tubules of the kidneys, and also eliminating waste material that will be carried off with the increased amount of urine that will thus be passed. The other view limits the amount of water, contending that one of the functions of the kidney is the elimination (secretion?) of water; to ask a damaged kidney to increase its function is to violate the principle of rest for a diseased organ. It is difficult to settle this question experimentally, and clinical observations are at variance. In contracted kidney the necessity for washing out the tubules and freeing them from large amounts of debris, such as is often seen in the parenchymatous types of disease, does not exist, nor is there, as a rule, a demonstrably great failure of elimination of solids. The total solids for twenty-four hours often reach the normal. What the toxic material is that is retained, or even if there be a primary retention toxæmia as the cause of the uræmic phenomena, is a question still not definitely settled. The necessity, therefore, for the huge amounts of fluids sometimes given these patients is not so clear as one might suppose, and a certain contra-indication seems to exist, from the fact that these large amounts demand extra work on the part of kidney, heart, and vessels, organs that one wishes to spare so far as possible.

The limitation of liquids to one and one-half liters per day, as is advocated by some, is perhaps wise, although too arbitrary. This is certainly not enough for many individuals. It seems better to allow some latitude in this respect, to say that one and a half to two liters per day is a fair average amount, but that a patient's own thirst may be a reasonably safe guide unless it lead to extremes, *e. g.*, one or two gallons per day. Some patients need explicit directions as to the amount of water to be taken; but no hard and fast rule can be given that is applicable to all. It is a good plan for all patients who

are taking only a fair amount of liquid, or an amount that is for them a restricted amount, to take occasionally larger amounts, say two to four quarts per day. This plan is in reality pursued by many who make trips several times a year to watering places. The same plan can be carried out at home by having, say, one day a week for a "flushing-out day," a plan advocated by von Noorden.

This limitation of the amount of fluids has been repeatedly advised by von Noorden and his pupils, and is supported by Pel, Koranyi, and many others. Some, however, like H. Strauss,[1] take issue with von Noorden and, on the basis of experience, advise against the too great reduction of fluids. The elimination of toxines and the dilution of the blood, even although there be an increase in œdema—as in parenchymatous forms—which in a measure is an eliminative process by which the blood is freed of toxic material, outweigh any supposed danger from increase in blood pressure.

Alcohol is to be avoided as an irritant of the kidney. This rule can seldom be violated with safety, for the temptation to excess is one not easily resisted by many. Occasionally a small amount of wine with meals may be allowed as a stimulant to the appetite and an aid to digestion, but the physician who permits this should know his patient well and be assured that there will be no excessive indulgence. Tea and coffee need not be interdicted. An excessive amount, however, may not only injure the kidney directly, but may have a harmful influence on the heart, vessels, and blood pressure. These beverages must, therefore, be taken in moderation. The same statements may be made concerning *tobacco*, the excessive use of which is to be avoided. But just as there is no necessity for depriving the one who is used to it of his morning cup of coffee, so there is no necessity of cutting off his after-dinner cigar.

Rules as to *diet*[2] in this disease must be general and quite flexible. Temperance and moderation as to food are to be enjoined. An excessive amount of food throws extra eliminative work on the kidney, tends to plethora, thus making unusual demands on the heart, and adds to the danger of disturbing digestion. Simple, easily digested foods should be the rule, and these should be taken with regularity, in reasonable amount, and without hurry. Rich and highly seasoned foods should be avoided. There should be but little used in the way of stimulating condiments, hot relishes, and sauces, pepper and other spices, mustard, radishes, cress, rich or strong cheese. Cakes, puddings, pies, pastries, candies—what are commonly classed as desserts or sweets—should be eaten sparingly, as disorder of the stomach and bowel is liable to follow their too free use.

A question on which there is much diversity of belief and of practice is

[1] *Berl. klin. Woch.*, May 25, 1908.

[2] Fuller details regarding diet in nephritis, and especially the question of meat as an article of food in this disease, may be found in the excellent discussion of the topic by Leube, in vol. vii of Penzoldt and Stintzing's *Handbuch der Therapie;* in the discussions by Senator, Ziemssen, and others in the *Verhandl. des IX Kongresses f. innere Medizin in Wien*, 1890, and in papers and discussions by Lépine, Grainger Stewart, and others before the International Medical Congress, Berlin, 1900. Diet was discussed in the *London Lancet*, in 1893, by several English writers, among others by Hale White, Ralfe, and Donkin. Much interesting clinical experience is found also in a symposium on the Treatment of Chronic Bright's Disease at the Britsh Medical Association and published in the *British Medical Journal*, October, 8, 1900.

the question as to what amount of *meat* should be allowed to the chronic nephritic. As the result of clinical observation and experiment, an excess of nitrogenous food has long been regarded as harmful in nephritis, whether one adopts the view of Semmola, that in nephritis the assimilation of nitrogenous food is interfered with and ingested albumin, therefore, is largely non-assimilated and merely adds to the task of elimination that is imposed upon the kidney, or holds that the excessive ingestion of albuminous food means excess of metabolic products, which must be eliminated by the already damaged organ. This view of the injurious effects of nitrogenous foods, of which meat serves as the type, has been widespread and has prevailed to such an extent that many nephritics have been entirely deprived of meats, eggs, and broths, and have had to depend exclusively on milk and the vegetables for the amount of proteid that is really essential for proper body nourishment. The fear of the injury to the renal epithelium from the greater amount of supposedly harmful extractives in dark meats has often led to their being absolutely forbidden. Many sufferers from nephritis, therefore, not only the parenchymatous types, acute and chronic, but from the chronic interstitial type as well, were compelled to forego nitrogenous foods, except milk, entirely, and the milk becoming distasteful, they really suffered from a poverty of albuminous foods. Lately there has been a reaction, an apparently justifiable reaction, against the too strict enforcement of the no-meat rule in nephritis. English, French, and American writers, and lately many of the German as well, now advocate the moderate use of meat, *i. e.*, a mixed diet, for the patient who is a sufferer from chronic nephritis. The rule must be modified in the case of acute nephritis or the acute exacerbations of the chronic disease.

The chronic nephritic cannot, without harm, be too long deprived of *proteid*. The amount estimated as necessary, about 80 to 90 grams, would require the drinking daily of over two liters of milk, or the taking of fifteen eggs, or 400 grams of meat. It seems far better to let this amount be taken not in the shape of milk alone, nor of meat or eggs, but, as said, in the way of a mixed diet, some milk, perhaps a liter, and a moderate amount of meat and eggs. Most patients, at least in this country, must be restricted very materially in the amount of meat taken, for, as a rule, they are heavy meat eaters, many taking it freely three times a day. Meat once a day, with an occasional egg, will be found not only not harmful, but really of benefit, helping appetite, increasing the strength, and improving the condition of the blood. This, with the liter of milk and the small amount of proteid contained in the other food taken, will furnish the amount of albuminous food necessary to meet the demands of the body, and to make up for the inconsiderable loss of albumin through the urine. Dark meats taken in these moderate amounts are not to be regarded as injurious. Whether meat is advised or not will naturally depend on whether it is well handled by the stomach and bowel. Harm may come from forcing the meat diet when it produces gastro-intestinal disturbances. Houghton[1] believes that when in the course of a nephritis characterized by high blood pressure there is indican in the urine, treatment designed to lessen the amount of proteid putrefaction in the bowel will have a tendency to lower the blood pressure by preventing the absorption of substances which, although rapidly eliminated with a normal kidney, are allowed

[1] *American Medicine*, October 7, 1905.

to accumulate in the blood and other organs of the body by reason of the reduced kidney capacity. Temporary removal of meat and eggs from the dietary will here be indicated.

Soups that are rich in meat extractives, such as contain an abundance of "stock," should be taken in moderate amounts only. Gruels and simpler soups may be taken more freely. Raw eggs are probably more harmful than cooked eggs,[1] although Leube justly observes that there are few people who by preference prefer raw eggs, and believes that the danger from taking a few uncooked eggs daily is not so very great.

To make up the caloric value necessary for an adult, considerable *carbohydrate and fat* must be taken in addition to the proteid. Of the latter enough is commonly ingested in the form of butter, cream, oil, and as a constituent of some of the other foods. The carbohydrate (300 to 400 grams) is supplied by cereals of various kinds, bread, vegetables, especially the young and green vegetables, and fruit. No especial limitations need be placed as to kind or amount of these foods. Asparagus is regarded by some as harmful, although it may probably be taken without injury, if not used to excess.

The dietetic treatment may be summed up in a few words by saying that the diet must be a mixed diet from which all highly seasoned, spiced foods and alcohol are excluded; meat and other proteids are to be taken in moderate or small amounts; cereals, vegetables, and fruits freely; the sweets sparingly. Milk is allowed freely, but neither it nor water is to be taken in excess for the supposed benefit that is to come from flushing out the kidneys. The total amount of food taken should not be excessive; the nephritic should not be a "heavy eater."

Physical overexertion is contra-indicated; not only does this act injuriously on the heart, that must be spared all unnecessary strain, but it makes a call upon the kidney to carry off an added amount of debris, the result of this excessive muscular exertion. Similarly, mental and nervous overwork may have to be curtailed. These injunctions as to less physical and nervous work, less worry and anxiety, are of great importance, but while easily given by the physician are often less easily obeyed by the patient. Intemperate habits as to hours of work, sleep, time given to social and other pleasures may have to be corrected. The keynote to the treatment in these respects, as in the matter of diet, is moderation. The patient with nephritis must have impressed upon him the fact that although he may be temperate as regards the use of alcohol, he may by intemperance in other respects, food, work, worry, etc., be doing himself as much harm as though he were indulging in alcohol to excess. Absolute rest in bed is seldom necessary for the patient with chronic interstitial nephritis, except during periods of acute exacerbation, cardiac failure, or in the later stages of the disease, unless it be, perhaps, when the patient first comes under the care of the physician, who may then deem it wise, in order to "get a line" on his patient, to put him to bed for a few days of careful observation. Physicians at times prescribe too much abstention from muscular exercise. The nephritic needs such exercise. Carefully regulated walking or gymnastics, or in selected cases massage, may be of benefit. Even mild and systematic mountain climbing, as practised by Oertel in his treatment of certain cases of heart disease, may

[1] Senator, *Berl. klin. Woch*, 1882, No. 49: Csátary, *Deut. Archiv f. klin. Med.*, 1891, xlvii, 179; Ott, *ibid.*, 1894, liii, 608.

not be contra-indicated. It is surprising how, at times, a patient who has been confined to the bed or to the house will, on being allowed moderate exercise in the open air, show improvement in muscular strength, heart tone, blood condition, appetite, and show no harmful effects in the work of the kidney as evidenced by the urine.

But relative rest, as above described, is of great importance. Business men must be encouraged to throw off some of their burdens upon younger shoulders, and instead of putting new irons into the fire, to take out a few. The yearly vacation should be lengthened, and, when possible, frequent trips away from business care should be taken, in which the main occupation should be idling, with mild exercise in the way of walking, golf, fishing, etc., rather than severer sport, such as rowing, mountain climbing, tennis, or similar pastimes calling for too severe muscular exertion.

This naturally leads one to consider the value of special *climates* and of watering places. The main value of the life at such watering places lies in the change from the former routine work of the patient, the rest and relaxation in which he indulges, and his greater care as to diet. The use of the waters, too, inducing free catharsis and diuresis, is, unless too long continued or too freely employed, of advantage, giving the patient the benefit of the "flushing-out" period, to which reference has been made. There is for this disease but little special virtue in any particular water. In general, the alkaline waters, or, with anæmia, the chalybeate waters, are to be preferred. Much of the advantage that comes from the water cure is dependent on the local conditions that prevail and upon the climate. Unless the patient is to have a reasonable degree of comfort, at least approaching that of his own home, he might better let well enough alone and not leave his pleasant bed and board. Oftentimes a plain, unvarnished talk with the patient regarding the water cure is advisable, for he may have the notion that is quite prevalent that if he can only go to this or that spring, the waters of which are good for diseases of the kidney or even curative, he will be at once greatly benefited or cured, and he is willing to make sacrifice of time, money, and comfort for the sake of being able to drink of these waters of marvellous virtue. It is due him to know, and a kindness is done by informing him, that a cure is not to be looked for, and that more is to be thought of in his going to the springs than the water alone; one must look into the matter of climate, surrounding country, food, sleeping accommodations, companions to be met at the resort, possible amusement, etc.

It is often better to disregard entirely the supposed water-cure feature and to have the patient go to some pleasant place or resort, for an outing and a period of rest. In winter a dry, warm climate is desirable, such as that of Southern Texas, New Mexico, Arizona, California, Mexico, Egypt, Southern Tirol, or the Riviera. In summer a cooler locality should be sought, and Canada, Northern Michigan or Wisconsin, the mountain regions of New England, New York, Virginia, or Colorado, may be sought, where there is the attraction of beautiful scenery and the advantage of pure air without too much heat. In the mountain regions, mountain climbing must be interdicted. Edel[1] finds in nephritics that the Alpine climate, especially when there is mountain climbing, increases blood pressure and is injurious. He believes, however, that in cyclic albuminuria the Alpine

[1] *Münch. med. Woch.*, 1904, li, No. 19.

climate is beneficial. In some of the mountain localities and in the Southwest, care must be taken that the patient is not thrown into too close contact with the tuberculous patients who are to be found there in great numbers, both because of the danger of his contracting tuberculosis, and because of the mental depression thus induced. He must be advised to guard against sudden changes in temperature and unnecessary exposure to cold when away from home, as well as when at home. Woollen underclothing or handy outer garments are great helps in this direction. As has been said in speaking of the treatment of the parenchymatous forms of nephritis, cold *baths* are to be avoided. And the home physician must caution his patient, before he goes away, against the too free use of baths often advised because of some supposed curative effect. The chronic nephritic, with his heart perhaps on the verge of breaking down, is one who must exercise considerable care in the way of taking baths which are too prolonged or too hot, as dangerous depressive effects on the heart are sometimes seen to follow too vigorous treatment of this kind; or there may be a sudden cerebral hemorrhage.

To the physician having in charge a patient with chronic interstitial nephritis there is no problem presented that is more important, yet at the same time more perplexing and difficult of solution in the individual case, than that of how rightly to treat the *heart*. Cardiac hypertrophy and vascular hypertonia are salutary conditions, compensating in a measure for the renal lesion; blood pressure must not, therefore, be allowed to become too low. On the other hand, extreme hypertrophy and excessively high blood pressure carry with them not only some unpleasant subjective symptoms, such as headache and dizziness, but constantly threaten such serious accidents as cerebral hemorrhage or cardiac incompetence and dilatation. How to steer the safe middle course between these two threatening conditions is indeed a perplexing question.

When the heart has given out and dyspnœa, cyanosis, œdema, and the other well-known symptoms and physical signs of incompetency are present, the general object of treatment is clearly to relieve the work of the overburdened heart as much as possible, and to use means to increase its efficiency. These patients should be put to bed for several days or weeks. The diet should be greatly reduced in bulk, a nourishing, concentrated food being taken, such as eggs, cream, or cereals. The bowels should be freely opened by cathartics. Digitalis in doses sufficient to produce a perceptible impression on the heart should be given. Patients apparently differ in their susceptibility to digitalis, and the preparations on the market are so varying in their strength and so often unreliable that it is difficult to say just what is a proper dose for a given patient. One must feel one's way with increasing doses until an impression is made on the heart and pulse, but must at the same time watch for the evidences of digitalis intoxication, such as bradycardia, bigeminal pulse, nausea, a restless delirium, etc., and promptly cut down the dose when the full effects or untoward effects are noticed. No drug is of such value under these conditions as digitalis, and yet no drug requires more judicial skill and trained experience for its proper use and for a correct interpretation of its effects. The tincture in doses of 5 to 15 drops, the infusion freshly prepared from the leaves, 1 to 4 drams (4 to 14 cc.), or the powdered extract, $\frac{1}{5}$ gr. to $\frac{1}{3}$ gr. (gm. 0.013 to 0.02), are what the writer most often uses. Digalen or digitalin may also be employed, particularly

when subcutaneous therapy is advisable. The results from the former used in this way or intravenously are sometimes excellent.

As substitutes for digitalis, strophanthus may be employed, and as adjuvants, caffeine or strychnine, or when prompt stimulating effects are needed, camphor may be employed hypodermically, from 1 to 3 grains (gm. 0.06 to 0.2) dissolved in 10 to 20 drops of olive oil, being injected perhaps several times a day. Venesection is at times of wonderful benefit under these circumstances; 300 to 500 cc. should ordinarily be removed, and occasionally this should be repeated in a few hours or more; even 500 to 700 cc. may be taken at the first bleeding. Baccelli[1] has advised a somewhat novel method of bleeding, using the dorsal vessel of the foot rather than the veins of the arm, as is common. Ice to the precordia may help check excessive palpitation, and morphine is often of great help, especially with pain, restlessness, and sleeplessness. The results from the treatment of cardiac incompetence can seldom be predicted. Oftentimes the breakdown of the heart is the beginning of the end. But it is remarkable how many of the patients whose condition seems truly desperate may with appropriate treatment be pulled together again, and how, with care, they may again enjoy months or perhaps years of comparatively fair health.

How best to treat the *high blood pressure* is a more difficult question. When it is present, the general rules as to diet, exercise, care of the bowels must be scrupulously lived up to. It is remarkable what may sometimes be accomplished in some of these cases by what may be called a temporary starvation plan of treatment, cutting down greatly the bulk of food taken, both solid and liquid, and employing concentrated but not bulky food, and not too much of that. Houghton's observations, already referred to, should be remembered. Blood pressure will sometimes under these circumstances be promptly lowered, and a general improvement in the condition of the patient will follow. Relative rest or perhaps even rest in bed for a time may be important. The bowels should be kept open, although not loose enough to make the patient feel weak. When the pressure is very high and accompanied by severe headache, dizziness, and sleeplessness, bloodletting will often give prompt relief for the time being. One may sometimes see marked improvement in subjective symptoms and quite a drop in blood pressure follow a spontaneous hemorrhage, such as a nose bleed; and the bleeding under these circumstances may be encouraged rather than checked.

Drugs for the lowering of blood pressure are rather uncertain in their results, at least so far as lasting results are concerned. Nitroglycerin, gr. $\frac{1}{100}$ to gr. $\frac{1}{40}$ (gm. 0.0006 to 0.0015), will, if given often enough, sometimes work wonderfully well. It must be given, however, not in any fixed dose, but in doses large enough to produce results, at times even gr. $\frac{1}{25}$ (gm. 0.0025) in one who has become habituated to its use. It is too often disappointing, results being nil, or a beating and throbbing headache follow the use of even small doses. The nitrites, *e. g.*, nitrite of sodium, gr. j to v (gm. 0.065 to 0.32), may be given in solution, the physician feeling his way with this remedy as he does with his nitroglycerin, and always beginning with a small dose. Potassium iodide in small doses, gr. v (gm. 0.32), may sometimes be given with advantage. In fact, it seems at times, when given for prolonged periods—months or years—to exert a very

[1] *Il Policlinico*, 1907, xiv, p. 18.

perceptible influence in softening the pulse and lowering blood pressure, and while one must realize that there is danger of serious effects in the way of iodism from the giving of too large doses in cases of chronic nephritis—the writer has seen a fatal case from such overdosing—one is justified in giving the remedy in these small doses and for a long time. It is, of course, wise to stop occasionally for a few days during this prolonged period, and not to give it without any interruption. The favorable effects that are occasionally seen in some cases—not necessarily the syphilitic ones—seem unquestioned, and this view is in accord with observations by such clinicians as Bartels, Senator, Semmola, and Grainger Stewart. Yet others, as, for instance, Aufrecht and Rosenstein, are skeptical regarding these good results, such as the retarding of the arteriosclerotic process, the lowering of blood pressure, and the avoiding in this way of some of the unpleasant symptoms, like angina and asthma, the result largely of secondary myocardial change. It has sometimes seemed that good has followed the use for a long time of Donovan's solution (liquor arsenii et hydrargyri iodidi) in small doses, one drop three times a day.

There is perhaps a tendency to use the vasodilators too early; although blood pressure may be high, this is not always an indication for the immediate adoption of measures for its relief; such high pressure may be a compensatory necessity. One is surprised at times to see improvement under digitalis, even when blood pressure is high.

The demands upon the kidney should be as light as possible, not only by regulating the kind and amount of food, the amount of physical and mental work, as already specified, but by striving to have the skin, lungs, and bowels do a part of the work of *elimination*. This has already been discussed in speaking of the treatment of parenchymatous nephritis, and need not be repeated here in any detail. Little can be done in the way of assisting elimination through the lungs save to keep up the action of the heart and to see to it that the patient has plenty of fresh air, both day and night. Daily warm or tepid baths should be taken to keep the skin in good condition, and those who have always been accustomed to the cool morning sponge bath will not be harmed by continuing in this way, being careful to avoid too severe or too prolonged chilling of the body, and being sure to secure the reaction shown by the glow of the skin that comes from the brisk rub-down. Occasional hot baths may be taken just before retiring. Sweats are not indicated, as a rule, unless uræmia is threatening or œdema is marked. When œdema is pronounced in this form of nephritis, it is, as a rule, due, as has been said, either to an exacerbation of the chronic process or to cardiac weakness. Under the latter circumstances sweats are to be used with great caution, for fear of aggravating the condition of the heart. The various methods of sweating are discussed under parenchymatous nephritis. The bowels should be kept open, although free catharsis is seldom necessary, save when severe uræmic conditions are threatening. Ordinarily, by regulating the diet, using plenty of fruit, green vegetables, coarser cereals, etc., the bowels may be made to move daily. When necessary, a morning saline purge may be given; or some of the vegetable laxatives, such as cascara, aloes, or senna, may be given at night. Elaterium, a brisk calomel purge, or large doses of the salines may be helpful when coma or convulsions seem threatening or drastic catharsis is for other reasons indicated. Enemas may be of service in regulating the bowels.

Venesection in the case of uræmia may be mentioned as an attempt to secure vicarious elimination when the kidney is failing in its function, as some toxic material is removed in this way.

Elimination through the avenue of the kidney itself, presumably the healthy parts of the kidney, is aimed at throughout the whole course of treatment, by regulations as to diet and drink, by keeping up the action of the heart, by the institution of "flushing-out" days, etc. Special efforts, however, are made in this direction by the use of diuretics, when, for any reason, the amount of urine or its content in solids is deficient. Digitalis and caffeine, acting largely through the heart, are of great value. Other remedies are the citrate and acetate of potassium and the sodium-theobromin-salicylate (diuretin). This latter remedy ought to be given fresh, before it has been long exposed to the atmosphere, and unaccompanied by any acid which renders it inert. In doses of 60 to 100 grains (gm. 4 to 6) daily it is sometimes an efficient diuretic. Its good effects are most often seen when the relative anuria is largely dependent on cardiac weakness, with resulting renal congestion. Lemonade containing cream of tartar may also be used as a diuretic drink, the cream of tartar being much more easily dissolved if hot water is employed.

Uræmia is discussed elsewhere in this volume, and only a bare outline, therefore, of its treatment will be given here. As a matter of fact, much of the treatment already described is in a sense the treatment of uræmia. Should uræmic coma or convulsions seem to threaten, as shown by the severe headache, vomiting, sleeplessness or delirium, dyspnœa, muscular twitching, the high blood pressure, with irritable heart and perhaps gallop rhythm, vigorous measures must be instituted. The patient is kept in bed, the bowels are opened by a colonic flushing, and a brisk purge of salts, calomel, or perhaps elaterium is given. A minimum amount of food is allowed for two or three days. Venesection will often give temporary relief, lessening the toxæmia, lowering blood pressure, and relieving some of the strain on the heart. Venesection may be followed by the use of normal salt solution, given subcutaneously, 500 to 1000 cc. *Lumbar puncture*, as recently advocated, will sometimes relieve symptoms temporarily. Just how this is brought about is not entirely clear, although the escape of a large amount of cerebrospinal fluid under high pressure serves to show that Traube's notion concerning uræmia has at least a color of truth. Digitalis and caffeine may be necessary, or, on the contrary, help may come from nitroglycerin. Morphine, while it has some disadvantages in the way of locking up secretions, is often indispensable. It relieves pain, restlessness, insomnia and delirium, helps to quiet the action of the heart, and at times actually seems to promote diuresis. Chloralamide is a favorite sedative with many. Convulsions may demand bromide or chloral, although morphine is more reliable and no more harmful. Chloroform is indicated when convulsive seizures are recurring frequently.

Œdema in chronic interstitial nephritis is not common. When it occurs, it is due either to the weakened condition of the heart, when it would be treated in the manner already outlined, or to an acute exacerbation of the chronic process. Its treatment under this latter circumstance would be that already described under acute and chronic parenchymatous nephritis.

Complicating conditions, or symptoms that become especially aggravated, may need special attention. The anæmia is often benefited by iron.

Basham's mixture, mistura ferri et ammoniæ acetatis, in doses up to ℥ss (14 cc.), is a non-irritating preparation that acts also as a diuretic. Tincture of the chloride of iron is less easily tolerated by the stomach, but when given in plenty of water after meals may be used in doses of five to thirty drops. Some regard iron, particularly in this form, as having a beneficial effect, not only on the anæmia, but on the nephritic process itself, a belief that is, however, not very widespread. The iodide of iron or any of the other preparations, such as Blaud's mass, or the scale preparations, may, if preferred, be employed. Anæmia is also combated by an abundance of fresh air, moderate exercise, and—a point of great importance—by seeing that in our endeavors to regulate the diet so as to suit it to the nephritic we are not really giving our patient food that qualitatively is improper and quantitatively is poor in caloric value. Relief of gastro-intestinal disturbances also contributes to improve the condition of the blood. Much stress ought to be laid on attention to the blood condition, not alone because when anæmia is marked such annoying symptoms as weakness, dizziness and palpitation become aggravated, but because with impoverished blood the power of the body to resist the disease becomes materially lessened, and the heart will not compensate as it should for deficiencies on the part of the kidney, which itself must be performing its function in an unsatisfactory manner, as, in fact, is true of all other organs of the body under these circumstances.

Careful attention to diet as specified, with the use of cathartics when necessary, will keep the alimentary tract in fair condition. In the later stages, however, *symptomatic treatment* will be demanded. Bitter tonics, as aids to appetite and digestion, may be indicated. The old-fashioned combination of tincture of nux vomica with hydrochloric acid will often serve a useful purpose. At times an acid condition of the stomach will be relieved by a few doses of soda or magnesia, or the mixture of rhubarb and soda. In some instances resorcin will relieve the distress from pressure and gas that follows eating. In extreme cases an abstinence from food for a day or two, with rectal feeding and enemata of salt solution, or the limiting of the diet for several days to the simplest articles, such as milk or rice water, will be necessary. Occasionally lavage gives relief. Hot applications or mustard plasters to the epigastrium may be tried when nausea, vomiting, and epigastric distress are extreme and unrelieved by dietetic measures, the use of stomachics, and aids to digestion. Bismuth, oxalate of cerium, drop doses of carbolic acid, and various other remedies may be tried to help quiet the rebellious stomach, but they are very unreliable. At times very minute doses of morphine by the stomach may be of service, or, what is better in the bad cases, a hypodermic of morphine, giving to the patient a quiet sleep and freedom for a few hours at least, from the persistent retching and vomiting, following which sleep he may be relieved for a time of the severe gastric distress. Diarrhœa is often benefited by giving a sharp purge of castor oil, salts, or calomel, followed by some of the vegetable astringents, such as tincture of kino. Tannigen in 5 grain doses may be of service. Like all the annoying symptoms due to uræmic intoxication, the vomiting and diarrhœa finally reach a stage where they are practically intractable, and their continuance adds not a little to the rapid progress of the disease.

Headache is relieved for a time by not overloading the stomach, keeping the bowels open, together with moderate exercise in the open air. But these simpler means will not quiet the suffering in the later stages. Here bromides

may be necessary or an occasional dose of one of the coal-tar preparations, *e. g.*, acetanilide, gr. iij (gm. 0.2), with perhaps $\frac{1}{3}$ or $\frac{1}{2}$ grain (gm. 0.02 to 0.03) of codeine. Care must be taken not to put these coal-tar preparations too freely into the hands of patients, as the habit of using them too often is easily acquired, and the effects on the blood, heart, and nervous system, as well as on the kidney itself, are often harmful. At times headache is relieved by lowering blood pressure by nitrites. The plethoric individual with high blood pressure may be bled. Later, morphine will have to be resorted to for the relief of the excruciating pain and to give sleep. Morphine is naturally a remedy that one should very rarely use in the earlier stages of chronic nephritis, because of its tendency to lessen secretions, and because of the danger of inducing morphinism. It is in the later stages of the disease, when the case is practically hopeless, that the greatest relief is afforded by this drug, which may be employed in the same way and for the same reasons that it is used in the later stages of carcinoma or of pulmonary tuberculosis, viz., to contribute to the comfort of one who is in the last stages of an incurable malady. The good that comes from the relief of pain, vomiting, nocturnal asthmatic dyspnœa, and sleeplessness more than makes up for any effect on the secretions or possible morphine habit of a few weeks' duration. Bromides, codeine, or heroin and other measures should, of course, be tried before resorting to morphine.

Other annoying symptoms must be treated according to the principles for their treatment under other circumstances. The same is true of the treatment of complications such as cerebral hemorrhage, pneumonia, or pleurisy. A word of caution is perhaps not out of order regarding the use of drugs that may seem indicated for these complications. Such drugs as salicylates, carbolic acid, alcohol, must be given with care, because of the danger of irritating the already injured kidney. The same may be said of the use of anæsthetics; anæsthesia in the case of the nephritic should be as brief as possible, and it should be realized that an exacerbation of a chronic nephritis is sometimes lighted up by the use of ether or chloroform.

The treatment of nephritis by supposed *specific* remedies, either in the way of drugs, sera, or such things as raw kidneys, seems to be wholly without good results.

Surgery, the decapsulation of, or incision into, the kidney, has been advocated of late as a means of treating nephritis. Some of the most ardent advocates of this procedure believe they are warranted in advising this operation in every case of chronic nephritis as soon as the diagnosis is made, provided the case is not practically in extremis, and provided, further, the proper skilled and experienced surgeon is at hand. There follows, Edebohls believed, an "arterial hyperæmization of the kidney. The result of this improved circulation in and between the tubules and glomeruli is the regenerative production of new epithelium capable of carrying on the secretory function." Comparison is instituted between this operation and the Talma operation for hepatic cirrhosis.

This comparison is a somewhat unfortunate one, as the Talma operation is by no means generally adopted by surgeons; is, in fact, largely given up because of the uncertain results. Nor has the great body of either surgeons or physicians fallen in with the surgical treatment of Bright's disease, although several years have elapsed since it was first discussed, and although experimental work and numerous operations on human beings—many

of these admittedly experimental—have been reported. As a routine treatment for chronic nephritis, it has not the support of the profession as the result of experience. And when we think of the nature of a chronic interstitial nephritis, for instance, with its local renal fibrosis, its widespread cardiovascular changes, the toxæmic origin of the condition, the influence of heredity, etc., it is difficult to understand how the improvement of the mechanical conditions in the kidney or even of its nutritional activity can work a cure. Temporary improvement is all one would expect, and, remembering the natural variability in symptoms in chronic nephritis, in the amount of albumin and casts, and noting, too, it must be added, the loose way in which diagnosis has been made in some of the cases recorded as instances of cure of chronic nephritis, one is forced to ask whether the recovery in some instances may not have been from an acute nephritis or possibly from some non-nephritic albuminuric condition, rather than from a supposed chronic nephritis.

In cases of acute nephritis and of congestion in which the kidney is swollen and the capsule tense, Harrison and others have advised a splitting of the capsule or its puncture for the relief of tension. Marked improvement has been seen to follow this procedure, although the well-known spontaneous recovery of most cases of acute nephritis makes one doubtful in a given case as to what benefit has really been derived from this particular treatment.

The conclusions of David Newman[1] represent, perhaps, the views of a surgeon who, while prepared to do a radical operation, is yet conservative. He says: "The conclusions I have come to regarding the efficiency of incision of the capsule or of cleavage of the cortex are: (1) That the operation gives marked relief to the renal pain of chronic Bright's disease. (2) That in cases of hemorrhage, in which the bleeding is practically limited to one side, the operation should be recommended, as it has been frequently followed by cessation of the hemorrhage in chronic Bright's disease. (3) In cases of movable kidney associated with albuminuria, hæmaturia, tube casts, or blood casts, when due to causes resulting from the displacement, after the operation of incision and fixation these symptoms disappear permanently, but when coincident with Bright's disease only temporary good is effected by operation. (4) Anuria, dropsy, and dyspnœa may be temporarily relieved in chronic Bright's disease, but a cure is not effected. (5) That in anuria with uræmic symptoms arising in the course of acute or subacute infective nephritis, free incision of the capsule and cortex, by relieving the tension and congestion of the parenchyma, enables the organ to resume its function, as shown by active secretion of urine from both kidneys after the operation.

In general, it may be said that the profession looks askance—and rightly—at the indiscriminate operation upon every patient who has albumin and casts in the urine, and while in individual cases operation may perhaps be justified, an operation upon every case of nephritis is to be condemned. More logical reasoning will have to be employed and more convincing statistics brought forth before it can be granted that a surgical cure has been wrought of a disease of the character of chronic nephritis.

[1] *British Medical Journal*, October 8, 1904, ii.

CHAPTER IX.

AMYLOID DISEASE OF THE KIDNEY (LARDACEOUS DISEASE OF THE KIDNEY).

By JAMES B. HERRICK, M.D.

In 1842 Rokitansky separated from the group of inflammations of the kidney, or Bright's disease as it was commonly called, the kidney to which he gave the name of *Speckniere*, so called from the bacon-like appearance of the cut section. The name "amyloid" was later applied by Virchow to the particular form of degeneration found in this kidney. That the name is a misnomer, as the substance is not starchy, has been shown by the failure to convert it into sugar, as well as by various other chemical tests. Nitrogen, for example, has been found in it, as well as sulphur; albumose has been derived from it, and leucin and tyrosin; so that it seems to be closely related, to, if not identical with, some of the albuminous bodies. But what is its mother substance, what its relation to hyalin and to histon, is not yet definitely settled. Nor is it clear in what way the amyloid material is deposited in the tissues by the blood, whether it is carried in soluble form and coagulated after lodging in the vessel wall, whether it is conveyed by the leukocytes in its ultimate condition and deposited as such, or whether, on the other hand, the blood merely serves as the carrier of some unknown substance that acts upon the tissues with the resulting production from these tissues of the amyloid body. These questions and others dealing with the nature and pathogenesis of the amyloid substance, while of interest, need not be fully discussed in an article dealing rather with the clinical aspects of amyloid degeneration as it affects the kidney.[1]

Etiology.—Rokitansky's observation that amyloid degeneration in general was found in connection with a cachectic state induced by chronic suppuration, syphilis, or tuberculosis, has been abundantly confirmed, as also his statement that it was, as a rule, a general process not limited to one organ, but appearing simultaneously in several, such as the liver, spleen, and kidney. Foremost among these etiological factors, the exact method of whose influence in producing amyloid degeneration is, however, not known, stands chronic suppuration, such as is seen in unhealed empyema of the chest, chronic osteomyelitis, pyelitis, bronchiectasis, etc. Tuberculosis, particularly chronic tuberculosis of the lung with extensive cavity formation, tuberculosis of the intestine, tuberculosis of bones and joints with fistulous

[1] In addition to standard text-books on pathology, among many other references that might be given, the following may be consulted on this topic: Rokitansky, *Handbuch der path. Anat.*, 1842, iii, 421; Virchow, *Arch. f. path. Anatomie*, etc., vi, viii, xi; S. Wilks, *Guy's Hospital Reports*, 1856, ii; Lubarsch, *Virchow's Archiv*, 1897, cl; Petrone, *Arch. de Méd. Expér.*, 1898, x; Davidsohn, *Virchow's Archiv*, cl; J. Nowak, *Ibid.*, cliii; Neuberg, *Verhandl. der Deutschen Patholog. Gesellschaft*, 1904.

communication with the surface, is another cause, perhaps, as some contend, the commonest one. But it is possible that tuberculosis per se has less special influence in the production of amyloid than has the accompanying secondary pyogenic infection, as is the case in phthisical cavities, and bone and joint tuberculosis with fistulæ. Syphilis is a third cause, especially late syphilis, the so-called tertiary form. Malarial cachexia, gout, lead poisoning, leukæmia, carcinoma, beriberi, hypertrophic cirrhosis of the liver, actinomycosis of bone, rickets (syphilis?) have been regarded as rare and occasional causal factors. For a few cases no cause has been discovered. The lessened frequency of amyloid of the kidney, as of other organs, is to be explained by the comparative rarity with which one meets with neglected suppurative processes. Modern surgery, with its asepsis, has materially reduced the number of cases of amyloid. The earlier recognition and more intelligent treatment by hygienic and medicinal measures, as well as by surgical, of tuberculous, syphilitic, and suppurative affections also contribute toward the eradication of amyloid disease. That pyogenic organisms have an influence in producing amyloid is known not alone from the oft observed association of this condition and suppuration, but from numerous experiments on lower animals, in which the injection of such organisms as *Staphylococcus pyogenes aureus* has been followed by amyloid. The rapidity with which this artificial amyloid has at times developed is surprising. Krawkow[1] saw amyloid in rabbits eleven days after inoculation.

That non-suppurative inflammation of the kidney may produce amyloid is by no means certain, yet chronic inflammatory and fibrotic changes in the kidney are not infrequently found associated with amyloid degeneration in this organ. Both conditions may be due to a common cause, such as chronic suppuration or tuberculosis. Or the nephritic process may be secondary to the nutritive disturbances induced in the kidney by the primary amyloid and to the reactive inflammation that follows such disturbances and the accompanying irritation. Or it is possible that in some instances the inflammation of the kidney occurs first and the amyloid in some not clearly understood way is the result. Some cases of contracted kidney with amyloid seem clearly of this latter type.

Age and *sex* seem to have little influence except as they predispose to the induction of the contributing causes. Males are oftener affected, and the period of young adult and middle life furnishes the greater number.

Pathological Anatomy.—The amyloid kidney is large, firm, and heavy. It may weigh 250 to 300 gm. Exceptions to this are seen when the amyloid degeneration is associated with a chronic indurative fibrosis, so that there is a combination of the amyloid degeneration and contracted kidney. Under these circumstances the kidney may be smaller than normal, granular, and to the naked eye resemble the kidney of chronic interstitial nephritis; the amyloid change may, perhaps, be seen only on microscopic examination. The increase in size, which is the rule, is regarded by some as due wholly to the accompanying changes that are identical with those of chronic parenchymatous nephritis (large white kidney). The kidney is pale, smooth, and the stellate veins stand out distinctly. The capsule strips readily except in case of association with fibrous changes. The section shows a smooth, glistening surface, with clear differentiation between the deep red pyramids

[1] *Centralbl. f. allg. Path.*, etc., May 20, 1895, vi.

and the wide, lighter, waxy-looking cortex. The glomeruli show distinctly, many of them "projecting like glistening dewdrops." Washed with a solution of iodine in potassic iodide (Lugol's solution), some of them stain a dark mahogany brown, thus showing the presence of the amyloid material. The same dark color may be made out in other regions, showing the walls of vessels involved, such as the afferent, efferent, and straight vessels. If dilute sulphuric acid be used in addition to the Lugol's solution, a violet or bluish tint is often obtained instead of the brownish red. Better results are sometimes obtained with the Lugol's solution if the surface to be tested is first freed of blood by washing with water, then acidified by being treated briefly with a little acetic acid, and then adding the iodine solution.

It is in the bloodvessels of the kidney—the muscular coat of the arteries especially—that the amyloid change is to be made out. The extent, however, to which the vessels are altered varies very much. Some kidneys, to the naked eye, seem quite normal, yet the microscope shows here and there a glomerulus that has been affected; in other kidneys the change is widespread, not only the glomerular vessels being quite generally involved, but the other vessels of the kidney, and perhaps even the membrane of the wall of the tubules, or the epithelial cells themselves. The glomerulus is first attacked and may be converted into a structureless, homogeneous, waxy-like ball. Not only is each affected glomerulus apt to show an irregular, patchy distribution of the amyloid changes in the capillary walls, but the different glomeruli are very unevenly affected, some being entirely destroyed by the obliteration of the lumen of the capillaries by the amyloid in the walls, the glomerular tuft being represented by the structureless mass already described, others showing slighter changes, a few coils only being involved, while still others, even in the immediate neighborhood, are to all appearances entirely normal. The microscopic contrast between amyloid and normal tissue is more clearly brought out by staining. The order of frequency with which the different vessels are affected is variously stated, all observers, however, agreeing that the glomerular vessels stand at the head of the list. The afferent arteries, the vasa recta, the efferent vessels, the intertubular capillaries and arteries of the medullary substance, the capillaries of the cortex are in irregular order, and, to varying degrees, also attacked. Even Bowman's capsule and the membrana propria of the tubules may show the change, and at times the epithelial cells themselves, either as they are in place lining the tubule, or as they have dropped off into the lumen of the tubule, give the peculiar staining reaction of amyloid. The interstitial tissue and the capsule of the kidney have been occasionally found to show the amyloid change.

The remainder of the kidney is seldom normal. Frequently, and especially when the kidney is macroscopically like the large white kidney, the changes are indistinguishable from those of chronic parenchymatous nephritis. Some round-cell infiltration and some increase in connective tissue, or an occasional hemorrhagic area, may be seen, proving that the process is in reality diffuse, but the chief lesions are those of the epithelium of the tubules, the glomeruli, and Bowman's capsule, the cells showing the same swollen, granular appearances, the same fatty degeneration described under chronic parenchymatous nephritis. Casts and granular debris may also be seen in the tubules. In other kidneys, as has been said, the interstitial changes and the development of fibrous tissue predominate, and the kidney might be

classed as chronic diffuse nephritis, chronic interstitial nephritis, or as granular atrophy. The contracted amyloid kidney is believed by some to be met with oftener when syphilis is the primary disease.

Along with the renal changes are to be found the lesions of the primary disease, the suppuration, tuberculosis, or syphilis. There is also an anæmia, sometimes quite pronounced, with its results in the pallor and fatty degeneration of various organs. Œdema is often present. Cardiac hypertrophy and arteriosclerosis are probably never the result of the amyloid disease of the kidney, but they are sometimes found in the cases in which amyloid is combined with chronic nephritis with induration, when the nephritic process has been primary or has begun at least before the advanced anæmia, cachexia, and malnutrition, due to the primary suppuration or to the amyloid, have made it impossible for hypertrophy or other compensatory processes to develop.

Lastly, amyloid degeneration of other organs is present. Very rarely the amyloid kidney alone has been found—in from 7 to 10 per cent. of cases.[1] Generally, however, similar changes are found in the spleen and liver and not infrequently in the suprarenal gland, the wall of the intestine, or even in the heart.

Symptoms and Diagnosis.—Mild cases cannot be recognized by any symptom or sign unless one by good luck finds a cast or mass of debris in the urine that gives the characteristic staining reaction of amyloid, a finding the occurrence of which is disputed by many. A suspicion that amyloid exists might arise if an efficient exciting cause is present in the shape of suppuration, syphilis or tuberculosis, and if the albuminuria and other urinary findings are not quite typical of simple nephritis. In more advanced cases the patient is anæmic and even cachectic in look. Œdema may be marked, even to the extent of hydrothorax and ascites. Disturbance of the stomach and bowels is often present, a diarrhœa being sometimes the result of the amyloid degeneration of the intestinal wall. The spleen is enlarged, hard, and palpable, as is the liver. The pulse is usually somewhat rapid, and is not of high tension. The heart is not hypertrophied. These facts, at variance with the ordinary findings in nephritis, should arouse the suspicion of amyloid, when there is present long-standing suppuration, tuberculosis, or inveterate syphilis. The anæmia through malnutrition seems to prevent the development of cardiac hypertrophy. In some cases amyloid in the vessels of the heart itself may contribute toward the interference with the nutrition of the myocardium; possibly amyloid degeneration of the adrenal may have some influence in preventing increase of blood pressure and of arteriosclerosis.

The *urine* is usually increased in amount, pale, of low specific gravity, clear, and with but little sediment. The solids are but little altered. It is rich in albumin, and Senator showed that the percentage of globulin was unusually high. Casts, especially hyaline and granular, are present, although not in such large numbers as the amount of albumin would lead one to expect. Blood is rare. Both the amount of urine and of albumin seem to be quite variable, and the specific gravity is sometimes not reduced. Even in the same patient there may be remarkable variations from day to day. Cases of amyloid of the kidney without albuminuria have been described.[2] The

[1] Cf. Rosenstein, *loc. cit.*, p. 393; also *Bull. Nordisk. Medic.*, Band xii, Heft 1.
[2] Cf. Straus, *Soc. Méd. des Hôpit.*, June 10, 1881.

irregular distribution of the amyloid process in the different vessels of the kidney and the varying degrees of inflammation combined with it, together with the influence of the primary disease, of diarrhœa, etc., account in a measure for the striking differences in the urinary findings of different cases, and may help to explain the peculiar irregularities. Yet some of these irregularities are extremely difficult to understand.

Leube[1] reports an interesting case of a boy with vertebral tuberculosis and abscess formation, in whom an enlarged, hard liver became manifest, and in whose urine no albumin was found, although daily examinations were made for weeks, as renal amyloid was suspected. At the autopsy there was found not only amyloid of the liver and spleen, but the microscope showed unmistakable amyloid of the glomeruli and vasa afferentia of the kidney, a condition in which one would expect albuminuria. Rosenstein reports a case in which there was no albumin, the amyloid being found in the straight medullary vessels, a finding in accord with the absence of albumin and the polyuria. Yet he cites cases of Litten, Wagner, and others, in which even with glomerular involvement there was no albumin, as in the case of Leube.

As a rule, with a reduction in the amount of urine in amyloid kidney from whatever cause, the percentage of albumin and the specific gravity are increased. Wagner has grouped the cases of amyloid into: (1) Those in which although amyloid of the kidney is present, as shown by autopsy findings, there is no polyuria and no albuminuria; (2) those with polyuria and albumin; (3) those in which the amount of urine is diminished and the amount of albumin marked. But these groupings are rather artificial. The statement of Lecorché, that unless there be inflammatory change, *i. e.*, nephritis, there will be no albumin, is not generally accepted as correct.

There is as much variation in the general appearance of the patient and in the constancy of the other symptoms as in the urine. Instead of the typically weak, pale, cachectic, emaciated individual, with the muddy complexion—this complexion regarded as quite characteristic by Grainger Stewart—and with the swellings of dropsy, the patient may be fairly strong, of ruddy complexion, fat, and with no dropsy. Dropsy, in fact, may never appear, although it is incorrect to regard it as some seem to do, as dependent wholly on the parenchymatous nephritis that may be present, or upon a failing heart. Its dependence upon the amyloid degeneration, perhaps the cachexia of this condition—hydrops cachecticorum—is proven by the fact that œdema is often seen in amyloid disease, when the kidney is not involved, *e. g.*, in cases of amyloid of the spleen and liver. While the color may, as just stated, exceptionally be fairly good, there is commonly a pallor, even although the musculature and fatty panniculus are well preserved. This is due to the secondary anæmia that is present.

Uræmia, at least uræmia to be recognized as such, is extremely rare. Death is usually from gradual wasting and exhaustion, or due to complicating conditions, such as pneumonia, pleurisy, or peritonitis. Coma, toward the end, is commoner than convulsions; and even when the amount of urine is greatly diminished or nearly suppressed, headaches, uræmic dyspnœa, and convulsions are rare, the condition resembling more the toxæmia of anuria than that of true uræmia. Retinitis is rare. When, however, the amyloid has been implanted on a kidney the seat of a chronic interstitial inflammation, the cardiovascular changes, the retinitis, and uræmia may be prominent.

[1] *Diagnose der inneren Krankheiten.*

It is thus seen that no clean-cut picture of amyloid disease of the kidney can be drawn. It is modified not alone by the extent and location of the amyloid in the kidney, but by the degree to which the kidney is involved in inflammation, by the symptoms and consequences of the original disease in the way of the disturbance in function of other organs than the kidney, and by the effect produced by the amyloid change in such organs as the liver, spleen, intestine and adrenal. It is often impossible to analyze symptoms and pick out those due to the primary disease, to the amyloid of the liver, spleen or intestine, to the nephritis, and those specially due to amyloid of the kidney. In fact, the amyloid kidney with its manifestations is often so much in the background as to be unrecognizable even when one is on the lookout for it. The writer agrees with Leube when he says that under all circumstances the diagnosis of amyloid kidney is difficult. The diagnostic features may be summed up much as they are by this same clinician, when he says that amyloid of the kidney is only to be diagnosed when the liver and spleen—or at least one of these two organs, especially the spleen—are enlarged and hard, as they are with amyloid degeneration; when at the same time there is a long-standing phthisis, suppuration, or syphilis; when the urine, although increased in amount, of low specific gravity, clear, and with but a faint sediment, is yet rich in albumin; and when the cardiovascular changes of chronic interstitial nephritis are lacking.

Prognosis.—Virchow[1] declared in 1885 that amyloid was incurable, that healing in the strict sense could not take place. Yet, clinically, the process seems at times to remain stationary, or it is believed entirely to disappear and that at least a functional recovery ensues. This possibility is given some support by the observations of Raehlmann,[2] who saw amyloid of the conjunctiva disappear. Neuberg contends that amyloid material is absorbable, and it is conceivable that such absorption might tend toward a partial healing, at least if such a process starts in before the amyloid change has become far advanced. Clinically, however, amyloid kidney when far enough advanced to be recognizable is almost invariably fatal. Death may, however, be delayed for many years, even five or ten. Yet in some instances a very rapid development of amyloid is seen. Much depends upon the underlying disease, its amenability to treatment, the gravity of the accompanying nephritis, and the condition of the stomach and bowels. Persistent diarrhœa, whether due to tuberculous ulcers of the intestine or to amyloid changes in the wall of the same, is exhausting and is not infrequently a cause of rapid loss of strength. Some think the course of amyloid of the kidney due to syphilis is more prolonged than when due to other causes, and that syphilitic amyloid offers a more favorable outlook. Tirard[3] states that the lung symptoms of pulmonary tuberculosis frequently undergo improvement with the development of the renal affection.

Treatment.—Treatment may be briefly discussed. It consists in the early treatment of the primary disease. The proper handling of this disease may prevent amyloid. Early treatment, even after amyloid has developed, may retard the progress of the renal disease and produce, for a time at least, a functional recovery. Surgical treatment and by hygiene and drugs, of such conditions as chronic empyema, pyelitis, osteomyelitis,

[1] *Berlin. klin. Woch.*, 1885, p. 813. [2] *Virchow's Archiv*, vol. lxxviii.
[3] *Albuminuria and Bright's Disease*, p. 247.

tuberculosis of the lungs, intestines, bones and joints, syphilis of bones, should, therefore, be as prompt as possible, and the decision as to the time and character of operation or other therapy should always be reached, with due weight being given the possibility of the occurrence of amyloid, or the influence of such treatment upon amyloid already existing. Fresh air, sunshine, and plenty of nourishing food are indicated as well for the original disease, perhaps tuberculosis, as for the anæmia and cachexia attending the amyloid. Tonics are often of value. Iron and arsenic are indicated, and may be given in any form desired. Blaud's mass with arsenic is an excellent combination. The syrup or the pill of the iodide of iron may also prove useful. Potassium iodide is, of course, helpful if the lesions of late syphilis are present. Vomiting and diarrhœa will demand care as to diet and probably the use of various remedies, such as bismuth, tannigen, kino, or even opium. But each case must be judged on its own merits, and the palliative and symptomatic treatment instituted that seems suited to the individual, after all that is possible has been done in the way of removing or improving the fundamental and original disease. Nephritis that accompanies must be treated as best one may, according to the rules for the treatment of that condition.

CHAPTER X.

THE BACTERIOLOGY OF THE INFECTIONS OF THE URINARY TRACT AND URINARY FINDINGS IN THESE CONDITIONS.

By THOMAS R. BROWN, M.D.

In no branch of medicine have greater advances been made during the last decade than in that of infections of the urinary tract. This has come, in part, from the development of better surgical methods, and in part from more careful clinical studies, but in the main it must be ascribed to the enormous advances made in the field of diagnosis of diseases of the urinary tract—an advance so marked that in many well-known diseases our whole conception of the underlying pathological process has undergone a complete metamorphosis. From the clinical side, the introduction of the cystoscope has done much to advance our knowledge, but even more valuable has been the information derived from the catheterization of the ureters, by means of which the study of the urine from each kidney has been rendered possible. The laboratory has done its share by determining the bacteriological flora of the infections of kidney, ureter, bladder, and urethra, and by determining with a considerable degree of precision the functional ability of each kidney, a matter of paramount importance when operation is under discussion. Before taking up the bacteriology of the infections of the kidney and ureter—pyelitis, pyelonephritis, pyonephrosis, tuberculosis of the kidney, perinephritis, paranephritis, ureteritis, etc.—it seems advisable to discuss the general question of urinary infections, taking up in order, although briefly, the diagnostic value of the cystoscope and of the ureteral catheter, the method of obtaining suitable specimens of urine from the bladder and from the kidney, chemical and microscopic tests of value in the diagnosis of renal and vesical diseases, the bacteriology of the urinary tract in health and in disease, and the tests by means of which the functional power of each kidney may be determined.

It is an undeniable fact that many diseases of the kidney are never diagnosed because a systematic urinary examination is neglected, and if this is insisted upon in every case, many of the vague diseases, febrile and afebrile, especially in childhood, would be recognized as referable to inflammations in the urinary tract; indeed, we feel that there are certain questions which should be asked in every case presented to us: Are we dealing with a healthy or a diseased kidney? If pathological, what is the nature of the disease, and what are the etiological factors involved? Are both sides affected or only one, and if unilateral, which side is diseased? In cases of unilateral inflammation, if operation of any kind is under discussion, can the other kidney successfully perform the necessary secretory and excretory functions? If

both kidneys are involved, one more than the other, is life possible with the less diseased kidney if it is desirable to remove the more diseased organ?

The ordinary means of diagnosis help but little to answer these questions, although palpation is of some value in a number of cases and inspection in a few. We must have recourse to some or all of the tests, which we shall discuss. When we realize that far more than half of the cases of renal infection are not diagnosed intra vitam, we recognize, in the first place, the necessity for making urinary examinations in all doubtful cases, febrile and otherwise, and, in the second place, the value of the instruments of precision and of the methods about to be described.

Cystoscopy.—The use of the cystoscope has added largely to our knowledge of urinary infections. Cystoscopy is an extremely simple procedure in the female. It may be done with the patient in the knee-chest position, or in the dorsal position with or without elevation of the pelvis; many cystoscopes are used, but no better instrument for the purpose has been devised than that of Howard Kelly. In the male the procedure is somewhat more difficult, but still comparatively easy, the Nitze or the Freudenberg instrument probably being as satisfactory as any others. The strictest asepsis is essential in either case; while, as a rule, anæsthesia is not necessary, it may be required in very neurotic patients, or in case of a very irritable bladder or urethra, in which class of cases Berkhardt and Polano distend the bladder with pure oxygen, as they believe it has a distinctly anæsthetic effect.

Besides giving in a unique way a perfect picture of the condition of the bladder, whether normal or pathological, its irritability or lack of irritability, its condition of distention or contraction, the presence of residual urine, foreign bodies, tumors, calculi, or communications with abscess cavities or with neighboring viscera, it also furnishes knowledge of great value as to the condition of the kidneys. The ureteral orifices can be carefully examined and deviations from the normal noted. The orifice may be gaping, invisible, or œdematous, as frequently seen in cases of calculus in the lower portions of the ureter, or it may be surrounded by an area of ulceration, as frequently seen in renal tuberculosis, while the discharge of pus or blood from the ureter may be recognized, and by this means the nature and site of the disease suggested, if not absolutely determined. It is also important to note the flow from each ureter; while normally, after the discharge of the first few cubic centimeters, the urine flows intermittently, in certain cases of hydronephrosis and pyonephrosis there is a continuous flow until the renal pelvis is emptied, and then a slow, sluggish dropping. When renal hæmaturia or pyuria is slight, it is difficult to make a diagnosis by cystoscopic examination alone, as the fluid from the ureter does not materially differ from that present in the bladder, while sometimes we are obliged to wait a few moments after cystoscopy to determine the character of the flow from the ureteral orifices, as the act of introducing the cystoscope occasionally produces a reflex inhibition of kidney secretion. To those skilled in cystoscopy, information of very great value may be obtained as to the nature of the disease from the appearance of the ureteral orifices.

Ureteral Catheterization.—Unquestionably the most valuable advance in renal diagnosis made in recent years has come from the catheterization of the ureters and segregation of the two urines. The process is somewhat difficult in the female, more difficult in the male, but it is absolutely essential in all cases of renal infection in which operation is under discussion, and

most important in all other cases of suspected renal infection, for by this means alone is it possible to compare the two kidneys, to make studies of the urine from the two sides, to determine the functional power of each kidney—in other words, to acquire that intimate knowledge of the pathological anatomy and secretory peculiarities of each kidney which is absolutely indispensable to the proper treatment of this important group of cases.

Some have suggested the use of catheters colored with vermilion or cinnabar lacquers, which are impermeable to the *x*-rays, and which are, therefore, useful in certain cases, especially in the localization of calculi, while in certain cases it is justifiable to catheterize the ureters through a bladder opened by suprapubic incision, as otherwise accurate diagnosis is impossible; while this latter procedure is rare, it is sometimes necessary in severe cases of vesical tuberculosis, where it is impossible otherwise to find the ureteral orifice, and Legueu has treated four patients by this method with very successful results. In introducing the catheter, we can tell much regarding stricture of the ureter, and also, by the use of a wax coating, as to the presence of calculus. Kelly has shown that there may be a reflux of air into the ureter through the air-distended bladder in the knee-breast posture, while Lewin, Goldschmidt, Guyon, and Courtade have demonstrated that in the case of certain animals a reflux of fluids is also possible; nevertheless, it is safe to assume that the bladder is water-tight under physiological conditions, although, of course, this is not so when bladder or ureter is diseased. Rovsing puts his entire faith in the cystoscope and the ureteral catheter, and to these he ascribes his great success in nephrectomy and the reduction of his mortality in this operation from 13 to 3 per cent. since the routine introduction of these methods of examination.

Urine Segregators.—The great weight of surgical and medical opinion is unquestionably against the use of urine segregators, which were introduced because of the difficulties of ureteral catheterization. These segregators are of two kinds, each devised to obtain separate urines from the kidneys, in one type an attempt being made to form a water-tight septum between the two ureteral orifices (as in the instrument of Luys and Cathelin), in the other to elevate the posterior wall of the bladder so as to make it act as the septum (as in the instrument of Harris). Luys, Cathelin, and others believe that this procedure is less difficult, less harmful, and just as useful as ureteral catheterization, but the great weight of authority is in favor of the latter method. Most investigators believe that it is impossible to absolutely segregate the two urines by any other method than ureteral catheterization. Tuffier, however, believes that this mode of examination has won a definite place for itself in the domain of renal diagnosis, while it is unquestionable that it is of value in cases where it is impossible to find the ureteral orifices.

The Method of Obtaining Specimens.—It is, of course, essential that uncontaminated urine should be obtained from the bladder in the case of cystitis, and preferably directly from the kidneys in the case of infections of that organ. Various methods have been devised for this purpose, all designed to obtain urine free from contamination. The method of H. A. Kelly is as follows in the case of the female: The vestibule of the vagina and the mouth of the urethra having been carefully cleansed with bichloride of mercury or other antiseptic solution, followed by a thorough washing off with sterile water, the lips of the urethra are pulled apart by traction on the labia, and a sterilized glass catheter with a sterilized rubber cuff about 10 cm. on its

distal end is introduced, the operator only touching the rubber cuff at about its middle. After the urine has flowed for a short time, so that if a few microörganisms have been introduced from the urethra they would have been washed out, the rubber cuff is withdrawn by traction on its distal end and from 10 to 20 cc. of urine collected in a sterile tube; the same method, with slight modifications, is available in the male, a metal or rubber catheter, of course, being substituted for the glass catheter. It is essential that the operator's hands should be rendered free from possible sources of contamination by the usual means, and a most satisfactory way to obtain this is by wearing a sterilized rubber glove, or sterilized finger-tips. The efficacy of this method has been shown by the fact that in fifty-two control experiments made by the writer upon normal cases, in all but one no culture was obtained, and in this one colony of a white staphylococcus grew in the plate. In most cases of cystitis (and the same applies to pyelitis and pyelonephritis) the microörganisms are present in very large numbers, besides which two examinations are made in every case. Some clinicians advise a thorough irrigation of the urethra beforehand with some antiseptic solution, followed with sterile water, while Melchior insists upon the use of a double catheter, consisting of two tubes, one gliding within the other, and with this instrument and a smaller one employed by Moullin, the catheter never comes in contact with the meatus or the mucous membrane.

In obtaining urine from the kidneys, the only satisfactory method is by ureteral catheterization. In this case a cystoscope is introduced into the bladder, and through this a sterile ureteral catheter with a rubber cuff on its distal end is introduced into the ureter and inserted as far as necessary toward the renal region; if simply a study of the urine is the object, the catheter should only be inserted a distance of one to two inches in the ureter, especially if the bladder shows signs of contamination; while if we also wish to determine the presence or absence of stricture, calculus, or pyo- or hydronephrosis, the catheter must be inserted a greater distance. Great care should be taken that the catheter touches nothing in its course and that the bladder is thoroughly washed out before its introduction, or at least carefully emptied. If there is infection of the bladder, great care should be taken; the bladder should be thoroughly washed out with some antiseptic solution, followed by repeated irrigations with sterile water; the ureteral orifice should be carefully swabbed with a solution of silver nitrate, and the catheter should be inserted but a short distance into the ureter. The success of this method of obtaining urine from the kidney is shown by the fact that in thirty-two control experiments carried out by the writer either upon perfectly normal individuals or on those with one normal kidney, but with infection of the other, and in some cases also associated with cystitis, only one showed any contamination, and that was readily recognized as before, only one colony growing from three loops of urine.

In obtaining specimens from the kidney, it is wise to advise the patient to drink rather copiously of water before the examination. It must also be remembered that the greatest care must be taken in both procedures to avoid trauma of any kind, although, notwithstanding this, chill, rise of temperature, and other symptoms may be met with occasionally after ureteral catheterization.

Chemical, Physical, and Microscopic Examination of the Urine.—After having obtained the urine, it is essential that within a very short time

the examination should be made. We will discuss in a subsequent section the examination of the specimens obtained synchronously from the two kidneys as to their functional powers.

The *reaction* should be tested in every case, because it tells us in a broad way, by its acidity, neutrality, or alkalinity, something regarding the character of the microörganisms causing the infection. Of course, in the examination of bladder specimens this may not give us information of great value, because, for example, if we meet with a pyelitis caused by a urea-decomposing microörganism, if the other kidney is normal the alkalinity of the urine from the infected side may be neutralized, diminished, or overcome by the urine from the healthy side. Besides the mere reaction of the urine, it is important in certain cases to determine the degree of the acidity, which may be done in a fairly satisfactory way by titration of the freshly obtained specimen with a decinormal solution of sodium hydroxide, phenolphthalein being used as the indicator. Although this method is not as reliable as certain others, it requires but little time and furnishes a very fair criterion of the degree of the acidity. Of course, when the kidneys are catheterized the acidity of each specimen should be determined separately. It is important to determine the reaction, because, in the first place, we may meet conditions simulating a cystitis but without infection, in which the condition is due to a urinary hyperacidity, probably of neuropathic origin, and, in the second place, because certain bacteria definitely increase the acidity of the urine, others definitely decrease it. As to the normal degree of acidity, upward of 100 investigations in normal individuals showed us that it requires about 25 cc. of the decinormal hydroxide solution to neutralize 100 cc. of urine; of course, under normal conditions we may meet with figures considerably higher or lower than these.

The *specific gravity* should be determined because of the frequency with which a low specific gravity is met with in pyelitis and pyelonephritis, while it is especially valuable to compare the specific gravity of the urine from each kidney in cases of supposed renal infection.

The test for *albumin* should always be made, because in a broad way it differentiates vesical from renal infections. Generally speaking, there is but little albumin in the case of a pure cystitis if the fresh specimen be examined, while, in the writer's opinion, although there are many who oppose this view, there is relatively an increase of albumin in pyelitis and almost always a definite increase in pyelonephritis. Speaking broadly, a marked disproportion between the grade of pyuria and of albuminuria speaks for cystitis, while, if considerable albumin is present, pyelitis is often present alone, or associated with cystitis. This point is of great importance, because the symptoms of pyelitis are frequently vague, and the first suggestion that a renal infection is present may come from noting the frequent or constant presence of a moderate degree of albuminuria. Rosenfeld states that the limit of the albumin content in the severest cystitis is 0.1 per cent.; in maximo, 0.15 per cent.; in pyelitis it is often 0.3 per cent., while Goldberg, who counted the red blood cells and determined the albumin quantitatively, concluded that if the ratio of the latter amount in percentage to the number of red corpuscles per cmm. is more than 1 to 30,000, there is true albuminuria, while if less than 1 to 30,000, the albumin is accounted for by the blood alone.

The *microscopic examination* is a matter of extreme importance and

should be made with great care. The centrifugalized specimen should be examined, and at the same time, by allowing a definite quantity of urine to stand a certain time, we learn something regarding the degree of infection, and the effect of any treatment we are employing may be roughly judged by the depth of this sediment. Especial attention should be paid to the presence or absence of *microörganisms*, *casts*, *pus cells*, *red blood cells*, and *epithelial cells*. As to the *microörganisms*, their number, motility, and morphology should be noted; stained specimens should always be made, and in every case in which there is the least suspicion of such infection, tubercle bacilli should be stained for; in cases in which bacteria are seen microscopically but the cultures are sterile, it is extremely important that anaërobic cultures be made, a point upon which Albarran and Cottet have especially insisted. In case of *blood* in the urine, the only way to exactly determine its source is by cystoscopy and ureteral catheterization; although some claim that marked crenation and loss of hæmoglobin suggest a renal origin, this is a most unreliable criterion. As regards *pus cells*, ureteral catheterization is essential in determining their source, although, if macroscopically the pus occurs mainly in the first portions of the urine catheterized, it speaks more for a vesical origin. The claim some make, that certain *epithelial cells* are peculiar to the pelvis of the kidney and the ureter, is entirely erroneous, because exactly similar cells may be met with in the lower epithelial layers of the bladder, and consequently may be met with in cases of pure cystitis. As a criterion of the effect of any treatment, the number of pus cells and red blood cells can be counted from time to time with a hæmatocytometer; pus and blood may also be determined by chemical methods, but this is obviously less satisfactory. Whether a few pus cells can be found in the urine under normal conditions, or when marked leukocytosis is present, has not been definitely determined, but Talma has described two cases in which such an origin is at least suggested.

Functional Activity of the Kidneys.—Within the past few years a great deal of work has been done upon the determination of the functional activity of the kidneys, for this determination is obviously of paramount importance when operation is under discussion. Various tests have been devised, this branch of diagnosis having been markedly developed by the careful work of Casper, Richter, Albarran, and Koranyi. In determining the functional ability of both kidneys from the mixed specimen, the two methods of most value are the determination of the amount of urea in the twenty-four-hour specimen and cryoscopy of the blood. As is well known, there is normally an excretion of about 30 grams during the twenty-four hours, and some believe that if the urea constantly runs less than 15 or 16 grams, a nephrectomy should not be done; in fact, the only operations to be considered should be those of absolute necessity.

In regard to *cryoscopy of the blood*, it is well known that the freezing point of this fluid is very constant, varying from —0.55° C. to —0.57° C., and that of all the factors that cause this to vary from normal, nothing is so important as diseases of the kidney. Kümmell and Rumpel have shown the value of blood cryoscopy in 300 cases of renal disease, and they conclude that, with a freezing point of —0.56° C. the kidney may be removed, while the farther the freezing point varies from this normal, the greater the danger of nephrectomy; if it is more than —0.6° C., nephrectomy should never be done; if the lowering of the freezing point of the blood is not within the normal limits, only the

essential operation should be done, such as incision of an abscess, removal of a stone, etc. Frisch also believes that blood cryoscopy is extremely valuable, while Rovsing puts little faith in it, as he has seen a great many exceptions to the rule, due to the many factors involved, apart from disturbances of kidney function.

The determination of the functional activity of the separate kidney is a matter of far greater importance, and this, of course, can only be done by ureteral catheterization, the urine being collected simultaneously for a short time from each kidney separately, and then the various tests made with the separate urines. There are obvious objections to this method, as Israel and others have shown that the functional activity of the kidney differs very markedly at different times; on the other hand, it unquestionably gives us information of great value, especially if the results are compared with the other findings. We must remember that the presence of a slight amount of albumin, or even a slight amount of pus, in the supposedly better kidney is not an absolute contra-indication for removal of the more diseased organ, and that a perfectly clear urine may come from a contracted kidney; if one concluded for that reason that the kidney was intact, serious results might follow nephrectomy. Of course, generally speaking, if the urine from the other kidney is free from albumin, blood, and pus, that kidney may, as a rule, be relied upon to perform the full renal function after the removal of its fellow, while the presence of pus and bacteria in the urine from the other kidney usually prohibits nephrectomy; on the other hand, the presence of albumin without pus and bacteria often simply means a transitory derangement of function, probably due to intoxication from the diseased kidney, and is certainly no definite contra-indication to operation.

The important tests to determine the functional activity of the separate kidneys are the cryoscopy of the urine, that is, the determination of its freezing point, the study of the elimination of colored substances, the determination of the urea and of the nitrogen, the phloridzin test, the test of the electrical conductivity of the urine, the determination of the toxicity of the urine, the determination of the amount and the specific gravity of the urine, the flexibility with which the kidney reacts to the taking of large quantities of fluid by mouth, and the determination of the quantity of chlorides and other salts normally present.

Functional Activity of the Separate Kidneys.—Although there is considerable discussion regarding the merits of the various tests to determine the functional activity of the separate kidneys, in all doubtful and in all serious cases it is wise to make use of some of these methods. Generally speaking, if a kidney is diseased or functionally disturbed, fewer molecules will be elaborated from the blood, and the kidney will show less tendency to react to various stimuli than a normal kidney, the degree of this divergence from the normal depending upon the extent of the lesion; for instance, when a considerable portion of the parenchyma is destroyed, the freezing point is low and the sugar secretion after phloridzin often entirely absent. The majority of clinicians pay considerable attention to these functional tests, although probably no one is absolutely diagnostic. According to Rovsing, the functional activity cannot be determined by any of the so-called functional tests, as the organ's activity may be temporarily reduced, especially by disease of the other kidney, while Israel also places little reliance on them, as he thinks the time is too short to warrant the

acceptance of the results as any index of the condition of the organ. On the other hand, many of the most careful investigators lay great stress upon the value of these tests, notably Albarran and the French school, and Casper, Richter, and many of the German investigators. Unquestionably the great improvement of results within recent years is due, in the main, to ureteral catheterization and study of the urine thus obtained, but some of the improvement must be referred to the study of the so-called functional tests of the separate kidneys.

The determination of *urea* is of great importance in this connection. If one kidney constantly shows a deficiency in urea excretion compared to the other, it suggests very strongly that the functional ability of the former is deficient. We must not forget, however, that, as Rovsing has insisted, the urea output of the kidney may be distinctly below normal, yet after the removal of its fellow, the urea secretion may become normal, as he showed in 31 of 112 cases of nephrectomy; he therefore insists that the test is only reliable when positive.

The determination of the *chlorides* and other mineral salts is resorted to but little, because of the many factors involved in their elimination.

The determination of the *reaction* of the urine from the separate kidneys is very interesting, because with an alkaline urine from the infected side the presence of an acid urine from the other kidney suggests that it has not become infected.

The determination of the *specific gravity* is also of value, a low specific gravity of the urine from one side compared with that from the other being very suggestive of disease of the former.

As regards the so-called *color excretion test*, there is considerable difference of opinion. It was formerly thought that after the subcutaneous or intramuscular injection of certain coloring reagents, such as methylene blue or indigo-carmine, in a short time an excretion of the coloring matter followed from the well, but not from the diseased, kidney. Rovsing, Casper, and others have shown that this test is absolutely unreliable, as the color may be secreted in parenchymatous or interstitial nephritis and other renal diseases, and for that reason the great value of this test is in aiding us to see the ureteral orifices and in determining definitely the presence of both kidneys.

Cryoscopy of the urine, or the determination of the freezing point, has unquestionably proven of real value when the two sides are examined simultaneously, and of very little value if the urine as a whole is examined. The freezing point is determined by the totality of molecules without reference to their quality, and if the kidney is diseased, or its function disturbed, fewer molecules will be elaborated from the blood, and the figures from the diseased side will differ considerably from those from the well side. This method was devised by Koranyi and is a comparatively easy one to carry out. Rovsing, however, regards it as unreliable, as he has found too many exceptions to the rule. Speaking generally, the lowering of the freezing point of one side points to disease of that side, while if the urine as a whole shows a constant lowering in a case of cystitis, it suggests very strongly the development of pyelitis.

The *phloridzin* test is another one which has been extensively used. It is well known that after giving phloridzin there is an excretion of sugar by the healthy kidney, while the more the kidney is diseased the less sugar excretion will take place. This test is unquestionably valuable when posi-

tive, for it rarely if ever happens that sugar excretion occurs when the kidney is extensively diseased, but Rovsing insists that it is unreliable when negative, since the healthy kidney sometimes fails to excrete sugar after phloridzin; he found this, for example, in eight of nine cases of renal tuberculosis, and yet after removal of the tuberculous kidney there was complete and immediate recovery.

The *dilution experiment*, as suggested by Illyes and Kovesi, is also of real value, for these investigators have shown that the water-secreting ability of the kidney suffers with the disease of its parenchyma. They give one to two liters of water a short time either before or immediately after catheterization; the urine is collected for from one to two hours from the two sides separately, and the quantity determined. With diseased kidneys, depending on the extent of disease, there is little or no increase of the secretion, and Albarran, who has also used this test extensively, insists upon its value, as the normal kidney is much more flexible in its reaction. The test of the *electric conductivity* of the urine has been used in a number of cases. It gives us in a satisfactory manner the molecular concentration of the urine, which is after all the object to be determined in many of the above-described tests. It is, however, not used to a great extent, because of the greater difficulties involved. The most satisfactory tests are those of the specific gravity, urea, water excretion, phloridzin, and freezing point, while the color excretion test is unquestionably of great value in finding the ureteral orifices.

Bacteriology of the Urine.—We shall next discuss the bacteriology of the urine in health and in disease, taking up in order the bacteria found in the normal urethra, in urethritis, in cystitis, in ureteritis, in pyelitis, pyelonephritis, and pyonephrosis; then the elimination of bacteria through the normal kidneys and the subject of bacteriuria, and finally, certain other interesting questions which suggest themselves, such as the pleomorphism of various bacteria, the agglutination of bacteria, and the treatment by sera and vaccines. Certain things should never be forgotten in making bacteriological examinations of the urine: first, the necessity of examining for the tubercle bacillus by the ordinary methods, and by animal inoculation in all doubtful cases, especially when the urine is acid and shows no growth on the ordinary culture media; and second, the necessity of making anaërobic cultures, if bacteria are seen in the stained centrifugalized specimens and no growth occurs on the ordinary media. Another point to be remembered is that in all cases of ureteral catheterization the catheter should be introduced into the ureter but a very short distance until it has been definitely determined that infection is present, after which, of course, the catheter can be introduced as far up as the renal pelvis. The conditions which predispose to the development of infections in various portions of the urinary tract will be discussed under a separate heading, as will also that of the mode of entrance of the bacteria.

The Bacteria of the Normal Urethra.—It is essential to consider these, because one of the common causes of cystitis is the introduction of some of these bacteria into the bladder by a catheter or other instrument. We may safely say that all the mucous membranes in contact with the air contain bacteria, and of these some will be pathogenic; thus, Melchior found the colon bacillus in the vulva of healthy women in half those examined; Bouchard and Charrin found this microörganism frequently in this location,

and it is probable that in a large number of cases the colon bacillus as well as other pathogenic bacteria are to be found in the vulva and the vestibule of the vagina in women and in the glans in the male, which is not at all an unexpected condition. As to the bacterial flora of the normal urethra much work has been done, and the results in the main have harmonized. All investigators have found many varieties of bacteria in the healthy urethra in both the male and female. Gawrowsky found many bacteria, including staphylococci and streptococci, a result agreed in by Posner and Lewin, Barlow, Franz, Melchior, Rovsing, and many others. Melchior found that if the orifice of the urethra be treated with 3 per cent. carbolic solution, bacteria were still present in the urine even if it was obtained by catheter, and only after very careful irrigation with boracic acid solution and subsequent catheterization could he obtain a urine free from bacteria. Kraus and Chvostek found bacteria in the urethra at a depth of 6 to 8 cm. in 60 per cent. of healthy males examined by them, while Schenk and Austerlitz found the urethra free in more than half the cases of normal women.

The different results obtained by different investigators depend unquestionably upon the different methods and the different surrounding conditions, but we may say that in the vast majority of cases of men and women, if not in all, the normal urethra contains bacteria of the most different kinds. The following bacteria have been found in the urethra: The colon bacillus, *Staphylococcus pyogenes aureus* and *albus*, various forms of streptococci, *Diplococcus candidus*, various forms of sarcina, leptothrix, *Streptococcus liquefaciens*, pseudogonococcus, smegma bacillus, pseudodiphtheria bacillus, *Diplococcus pyogenes*, and many others. Of course, these are probably not all different species, as the same microörganisms have undoubtedly been described under different names; nevertheless, these will show the extreme wealth in bacteria of the normal urethra, while of the pathogenic forms, such as the colon bacillus or staphylococci, in other words bacteria which can cause cystitis, Melchior has shown that they are present in more than half of the normal urethras.

These figures show the importance of the urethra as a source of infection of the urinary tract, and accentuate the necessity of extreme care in introducing catheters and other instruments; whether there can be a direct extension from the urethra into the bladder without instrumentation will be discussed under a subsequent section.

Bacteriology of Urethritis.—This is commonly regarded as the same as the question of infection of the urethra with the gonococcus. Nevertheless, it must be remembered that although this is the cause of infection in the vast majority of the cases, we may have a urethritis due to other forms of bacteria. Thus, it has been shown by Legrain, Kraus, Grosz, and others that an experimental urethritis generally lasting several days may be brought about by the introduction into the urethra of various bacteria, especially various forms of staphylococci and diplococci. Among bacteria other than the gonococcus which have been described as causative factors in urethritis may be mentioned various forms of diplococci and monococci, the *Streptococcus pyogenes*, *Micrococcus cereus albus*, *Bacillus coli communis*, *Staphylococcus pyogenes aureus* and *albus*, *Staphylococcus non-liquefaciens*, tubercle bacillus, etc., while it is not at all uncommon as a sequel of gonorrhœa to find a condition of bacteriorrhœa in which the urine shows large

numbers of organisms of different forms—bacilli, cocci, diplococci, etc.—which unquestionably tend to keep up the inflammation.

Bacteriology of Cystitis.—The bacteriology of infections of the bladder has for obvious reasons been studied far more thoroughly than the infections of any other portion of the urinary tract. A thorough knowledge of this question is essential to properly appreciate the various infections of the kidney, because, as we shall see later, in a large number of cases this is secondary to vesical infection. Before taking up the bacteriological findings in cystitis it will be well to discuss briefly certain questions of importance in this connection, such as the mode of entrance of the bacteria, the predisposing causes of infection, and various other etiological factors.

As regards the *mode of entrance* of infection in the bladder, this may be through the urethra either from the organisms usually present, or from bacteria present on an instrument used; we may have a descending infection from the kidney; we may have an infection by direct transmission from the intestinal tract; we may have an infection carried by the blood stream to the bladder, or a direct extension from some inflammatory focus localized in the pelvis or the lower portion of the abdomen. Examples of all of these modes of infection occur, but infection from the urethra, from instrumentation, or from direct extension is the commonest. Casper has shown that infection from the intestine is especially liable to occur if there is a slight lesion or congestion of the intestinal wall, while others have shown that in the case of diarrhœa or other intestinal disturbance bladder infections are more liable to occur.

In looking over the bacteriological findings in cystitis one is at once struck by the fact that in a great number of cases microörganisms are found which, as a rule, possess but slight pathogenic properties, and it would, therefore, seem probable that other etiological factors play an important role in the causation of cystitis. The function of the bladder epithelium is purely protective, and it is still a moot question whether absorption is possible from the healthy bladder. Some, such as Duval, Guinard, Boyer, and others, from their experiments on the cadaver and on the dog, believe that no absorption takes place, while others, such as Bazy and Sabatier, believe that it is possible. However, experiments have shown that the healthy vesical epithelium is extremely resistant to infection; thus, Guyon, Barlow, and others have shown that various bacteria may be injected into the bladder of animals without the development of cystitis, but infection occurs if the bladder mucous membrane be harmed or the urethra ligated. Bastianelli and Schnitzler have performed similar experiments, using the colon bacillus, the tubercle bacillus, the gonococcus, and various staphylococci and diplococci, and have obtained similar results; they found, however, that in the case of *Bacillus proteus*, which decomposes the urine and renders it alkaline or ammoniacal, no other factor was necessary. Melchior also found in the case of rabbits that although bacteria introduced into the healthy bladder did not produce cystitis, yet an inflammation could be set up by the application of cold to the pubic region, by the injection of hot or cold water, or by artificial trauma, results similar to those obtained by Bumm in the case of the gonococcus and by Rovsing in the case of a large number of bacteria.

Among the more important factors which predispose to cystitis may be mentioned the presence of ammonia in the urine, which is usually due to the *Bacillus proteus* or other bacteria which decompose urea, various conditions

which interfere with the bladder function and tend to impair its vitality, such as injuries and diseases of the nerves of the bladder, as in paraplegia and myelitis, congestion of the mucous membrane, especially the trigonal area, which may be caused by cantharides, toluidin, or other irritating chemicals, a urine of excessive acidity, straining of long duration, pressure, or obstruction to the flow of urine. The congestion met with at the menstrual epoch and during pregnancy, excessive cold or heat, and everything that prevents a complete emptying of the bladder, various factors which cause injury or trauma to the bladder, such as instrumentation, catheterization, operation or calculus, adhesions between the bladder and other organs, neoplasms, and general conditions, such as malnutrition, anæmia, arteriosclerosis, great depression and fatigue, which lower the resistance of the body as a whole, and consequently of the bladder as well, may also play a part.

The bacteriology of cystitis has a great interest historically, because Pasteur, in 1859, suggested that bacteria were the cause of urinary decomposition. It was not, however, until 1887 that Clado isolated his *bactérie septique de la vessie* as the cause of cystitis, and the same year Hallé described a short non-liquefying bacillus as the cause. Albarran and Hallé found this bacillus in 47 of 50 cases of urinary infection, calling it *bactérie pyogène*, producing cystitis in animals by its introduction if the urethra was ligated. Later this bacterium, which was found by many other investigators in urinary infections, was found to be identical with the colon bacillus. One of the striking features of the bacteriology of cystitis is that, while in the early days many bacteria were described and special names given to them, we now recognize that many of these were species of the same bacterium in which slight cultural differences were produced by differences in environment, thus, Clado's *bactérie septique*, Krogius' *bacille non-liquefiant*, Morelle and Deny's *Bacillus lactis aërogenes* probably, and Rovsing's *Coccobacillus ureæ pyogenes* are all probably but varieties of the colon bacillus, while the *Bacterium vulgare* and the *Urobacillus liquefaciens septicus* are identical with the *Bacillus proteus vulgaris* of Hauser. Marked polymorphism as regards motility and cultural peculiarities may be produced in the case of the colon bacillus by variations in the culture medium and in environment, and also marked changes in the staphylococcus as regards grouping and chromogenic properties appear under similar conditions; it is therefore not at all surprising that a large number of different bacteria and cocci have been described.

Rovsing, in a long series of cases of urinary infections, divided his cases of cystitis into the catarrhal and the suppurative forms, the latter being again subdivided into the ammoniacal and the acid. It is questionable, however, if the catarrhal cystitis which he describes is any other than a suppurative cystitis in which pus cells have been destroyed by the ammonia. Rovsing believed that acid cystitis is invariably due to the tubercle bacillus, a most erroneous view. In 1890 Krogius found his *Urobacillus liquefaciens septicus* in 3 of 10 cases of cystitis, while Schnitzler found the same bacillus in 24 cases of cystitis with ammoniacal urine, in 16 in pure culture; this bacillus is identical with the proteus of Hauser. Lundstrom, in 1890, isolated *Staphylococcus ureæ candidus* and *liquefaciens* from alkaline cystitis, and *Streptococcus pyogenes* from acid cases; Krogius found the colon bacillus in 16 of 22 cases, 14 in pure culture, while Rostoski from 120 cases

from the literature found the colon bacillus 80 times, proteus 11 times, and tubercle and typhoid bacilli, streptococci, and various micrococci, including the gonococcus, in a few cases.

Albarran, Hallé, and Legrain, in 1898, collected 304 cases from the literature, and found in 131 the colon bacillus, 89 times in pure culture; other microörganisms found were *Bacillus proteus*, *Streptococcus pyogenes* (18 times), gonococcus and tubercle bacillus, while among the rare bacteria were the typhoid bacillus, the diplococci of Fränkel and of Friedländer, *Bacillus longus ureæ*, *Bacillus crassus*, streptobacillus, urobacillus, coccobacillus, *Micrococcus subflavus*, and *Sarcina alba*. Among rare causes of cystitis may be mentioned the pseudodiphtheria bacillus, the *Bacillus pyocyaneus*, influenza bacillus, *Filaria sanguinis hominis*, bilharzia, echinococcus, various forms of yeast, and *Amœba coli*. In recent years Escherich, Trumpp, Haushalter, Finkelstein, and many others have called attention to the frequency with which cystitis due to the colon bacillus is met with in children, especially in association with various gastro-intestinal diseases. Bastinelli has isolated the pneumococcus in cystitis; Barlow, Wertheim, and others the gonococcus in pure culture.

Melchior, in 72 cases, found the colon bacillus 37 times (29 in pure culture); *Streptococcus pyogenes* in 4 (3); proteus of Hauser, 10 (4); tubercle bacillus, 4 (3); *Diplococcus ureæ liquefaciens*, 14 (11); *Staphylococcus ureæ liquefaciens*, 3 (1); *Streptococcus anthracoides* 3, (0); gonococcus, 2 (2); typhoid bacillus, 1 (1); *Staphylococcus pyogenes aureus*, 4 (3); and coccobacillus, 1 (1). He found, as the vast majority of other investigators have, that in most cases the urine is acid; in fact, with the exception of the proteus and a few species of micrococci, such as the *Micrococcus ureæ liquefaciens*, the urine is invariably acid; the frequency with which Rovsing found alkaline or ammoniacal urine is probably due to the fact that a large proportion of his cases were in old men with enlarged prostate, while Schnitzler's high percentage of alkaline cases is due to the fact that most of them were in cases of malignant disease, in which the proteus bacillus seems to thrive peculiarly well. Moullin, in 30 cases of cystitis, found the urine acid or neutral in 24, alkaline in 6; he found the colon bacillus 25 times (14 in pure culture), proteus bacillus 5 times, and the *Streptococcus pyogenes* 7 times.

Albarran and Cottet found one species of bacillus and two of cocci in anaërobic cultures, a very important finding and one that should suggest the advisability of making anaërobic cultures much more often than we do, especially when the microscope shows us bacteria which cannot be identified in the subsequent cultures.

Personal researches into the bacteriology of cystitis, published in 1899, showed in 26 cases of acute cystitis the colon bacillus in 15, the *Staphylococcus pyogenes albus* in 5 and *aureus* in 2, *Bacillus pyocyaneus*, typhoid bacillus, proteus bacillus, and an organism resembling in many respects the colon bacillus, 1 each, while in chronic cases the bacteriological findings were tubercle bacillus in 6, colon bacillus in 16, *Staphylococcus pyogenes aureus* in 3 and *albus* in 2, a bacillus resembling the colon bacillus in 1, the white staphylococcus, which decomposes urea, in 4, *Bacillus proteus* in 1, while in 2 cases the cultures, both aërobic and anaërobic, were negative. The comparison of the bacteria found in the acute and chronic cases shows no greater prevalence of the colon bacillus in the chronic than in the acute cases, which is important in that certain investigators claim that the colon

bacillus frequently enters in after the development of the cystitis and drives out the other bacteria. In these cases the microörganism was met with in pure culture in all but one of the cases, in which case the colon bacillus and the tubercle bacillus were associated. Thus, in the 60 cases of cystitis in which bacteria were found, the colon bacillus was found in 31, the *Staphylococcus pyogenes albus* in 7, tubercle bacillus in 6, the *Staphylococcus pyogenes aureus* in 5, the white staphylococcus, which decomposes urea, in 4, proteus bacillus in 2, and the typhoid bacillus, pyocyaneus bacillus, and unidentified bacillus, resembling in many respects colon bacillus, in 1 each. The urine was acid in the case of all the bacilli except *Bacillus proteus*, was generally acid, occasionally neutral, and very rarely slightly alkaline in the case of the *Staphylococcus pyogenes albus* and *aureus*, and alkaline or ammoniacal in the case of the white urea-decomposing staphylococcus and the *Bacillus proteus*. This series of cases consisted exclusively of women, and a comparison of the results found by others in men and in women shows that the colon bacillus is somewhat more prevalent in women than in men, while the less common forms are more likely to be found in men.

Thus, the cases of cystitis may be divided in various ways, first, as to whether the urine is acid or alkaline; second, as to whether one species of bacteria is met with in pure culture, which is the commonest occurrence, or whether two or more species are present; third, whether the microörganism met with is a bacillus or a coccus; and fourth, and probably the most satisfactory division, that into cases due to bacteria frequently met with, rarely met with, and those forms described by single authors, or saprophytic bacteria. Of the frequent bacteria may be mentioned the colon bacillus, the proteus bacillus, various forms of *Staphylococcus pyogenes*, *Streptococcus pyogenes*, gonococcus, tubercle bacillus, white urea-decomposing diplococcus or staphylococcus, possibly the typhoid bacillus and the streptobacillus anthracoides; of the rare forms may be mentioned *Bacillus pyocyaneus*, the diplococcus of Fränkel and of Friedländer, yeast, sarcina alba, etc.; while in the third group—that is, bacteria described by single authors, or saprophytic bacteria—a group which is being constantly reduced by identification with other bacteria, are to be found the various bacteria not identical with any known form, but which are in many cases in all probability varieties of well-known bacilli, staphylococci, streptococci, etc., which have been described under various names.

The Bacteriology of Ureteritis.—This is practically the same as cystitis on the one hand and pyelitis on the other, for in the vast majority of cases the ureter becomes infected either from an ascending infection from the bladder or from a descending infection from the renal pelvis. It must be remembered, however, that in exceptional instances the ureter may become infected from some contiguous focus of inflammation, and cases have been reported in which a ureteritis has directly followed an acute appendicitis or an appendicular abscess. The ureteral epithelium is, like that of the bladder, very resistant to infection, and unquestionably many bacteria may pass down the ureter, if in a healthy condition, without setting up an inflammation. If, on the other hand, the ureter is not normal, but is congested, dilated, or constricted, due to pressure, as from the pregnant uterus, or is diseased because of contiguous disease, its chance of infection is markedly increased. We may have, of course, only the lower portion or only the upper portion affected, while as to the bacteria which cause these infections,

they are obviously the same as those met with in cystitis or pyelitis, although no special studies have, for obvious reasons, been made of the ureter alone.

Bacteriology of Pyelitis, Pyelonephritis, and Infections of the Kidney.—Most of the tables of the bacteria found in pyelitis are of very little value, because the urine has been obtained from the bladder and not directly from the kidney by ureteral catheterization. Within recent years, however, this latter method has been used and, although the number of cases is comparatively small, nevertheless we know the microörganisms most likely to be found in infections of the renal pelvis or of the kidney itself. The question of whether the normal kidney can eliminate bacteria, and whether bacteria can pass through the kidney in various infections and inflammatory diseases will be discussed subsequently. As to the source of infection, we may have an ascending infection from the bladder up the ureter, the kidney may become infected from the intestinal tract, the bacteria being carried by the blood or by the lymph current; infection of the kidney may be but a part of a general infection, or bacteria may be carried from some nearby focus of infection, such as an abscess cavity, by the blood or lymph current, or by direct extension.

The bacteria found in our series of 20 cases of pyelitis and pyelonephritis, in which the urine was obtained by ureteral catheterization, were as follows: Of 3 acute cases, in 2 with acid urine, bacillus coli was found once and the tubercle bacillus once, and in the 1 case with alkaline urine bacillus proteus; of 17 chronic cases, in 12 with acid urine the colon bacillus was found in 6, the tubercle bacillus in 5, and in 1 case no bacteria were found, while in 5 cases of alkaline urine the proteus bacillus was found in 3, and the white urea-decomposing staphylococcus in 2 cases. In all the chronic cases with alkaline urine a stone was found in the renal pelvis, and in several cases in which cultures were made from the centre of the stone the microörganism was found which was the cause of the pyelitis, suggesting that the cause of stone formation is primarily a mass of agglutinated bacteria about which the salts precipitated in the alkaline urine are deposited. In each case, both acute and chronic, the microörganisms were present in pure culture.

The presence of accessory factors is far more difficult to determine in the kidney than in the bladder, but the fact that the condition is more likely to occur in people who are run down, anæmic, or depleted by various diseases, or in whom there is a condition of stasis of urine due to pressure upon the ureter by a tumor or pregnant uterus, or by constriction of the ureter due to adhesions, or in whom the kidney is congested, suggests that here also accessory factors play an important role. Why one kidney should be affected and not the other is in most cases impossible to say, but it is suggestive that in two of this series the kidney affected was markedly displaced, while in one case an operation, nephropexy, had been performed a few days previously. As to the mode of infection, in 6 cases of this series the infection was undoubtedly ascending, and in 7 hæmatogenous as far as one could tell; in the tuberculous cases 2 were unquestionably hæmatogenous in origin, while in the other 4 it was impossible to tell, although clinically the bladder symptoms made their appearance first. However, the weight of evidence is in favor of a hæmatogenous origin in the vast majority of cases of tuberculosis of the kidney. The study of these cases suggested that if the kidney became infected first the bladder as a whole showed fewer lesions than if the bladder was affected first and the kidney secondarily.

Krogius has found bacillus coli 6 times in pyelonephritis associated with cystitis, while Rovsing found the colon bacillus 19 times in pure culture, once with staphylococci and once with streptococci, in 21 cases of pyelitis not associated with cystitis; of 11 cases of pyelitis complicated with cystitis with ammoniacal urine, in 3 *Staphylococcus aureus* was found in pure culture, in 2 *Staphylococcus albus* in pure culture, and in 1 associated with the *Streptococcus pyogenes*, once with the *Bacillus proteus*, and in 1 case each in pure culture, the *Bacillus liquefaciens*, *Bacillus longus liquefaciens* and *Sarcina flava*, and in 1 case the colon bacillus in association with the *Streptococcus ureæ;* of 3 cases of pyelitis complicated with cystitis with acid urine, in 2 the tubercle bacillus was found, and in 1 the typhoid bacillus was found, each in pure culture. Melchior, in 5 cases of pure pyelonephritis in females, found the colon bacillus, the typhoid bacillus, and the *Streptococcus pyogenes* once each in pure culture, and in 2 in males the colon bacillus and the *Streptococcus pyogenes* once each in pure culture. A comparison between bacteria found in pyelonephritis in women and in men shows that about the same bacteria are found in each, but that the colon bacillus is unquestionably more frequent in women. Various rare parasites have been found in the kidney, and among these may be mentioned the *Eustrongylus gigas*, *Distoma hæmatobium* (bilharzia), actinomyces, filaria, and echinococcus.

Albarran, Tuffier, Schmidt, Aschoff, and Savor have shown the importance of the colon bacillus in infections of the upper urinary tract, while Melchior has shown that, if the colon bacillus is injected into the bladder and trauma produced or retention caused, in addition to the cystitis he could produce pyelitis, pyelonephritis, abscess of the kidney, and suppurative nephritis, and that in certain cases the colon bacillus was even found in the circulating blood. The consideration of bacteriuria shows us, however, that in a large number of cases the colon bacillus is able to pass through the kidney without producing any appreciable harm. Von Albeck has recently called attention to the frequency with which the colon bacillus is found in the urine of pregnant women, and he thinks that the pressure of the pregnant uterus upon the ureter and the consequent stasis of urine is the main cause of the pyelitis met with so frequently in pregnancy.

Bacteriuria.—This is the condition in which the urine becomes infected without any lesion of the urinary tract. The epithelium of the urinary tract is extremely resistant to infection, as shown not only by numerous clinical observations, but by many animal experiments. In addition, the normal urine possesses very distinct bactericidal properties, as Lehmann, Richter, Rostoski, and others have shown. These investigators have shown that the urine is bactericidal to the cholera bacillus and the anthrax bacillus to a considerable extent, and to a less extent to the colon, typhoid, and proteus bacilli; they all agree that this property is largely dependent upon the degree of acidity which the urine shows.

Whether the normal urine does or does not contain bacteria has always been a matter of discussion, many investigators holding that it does not, while many others contend that it does. The weight of evidence, however, certainly points to the belief that the urine of healthy individuals, if obtained under careful precautions, contains no bacteria, and in 88 observations on healthy human beings the writer did not find bacteria in the urine in any case.

In infectious diseases, however, unquestionably bacteria can be found in the urine, as in typhoid fever, in which the bacilli are found in the urine in from 20 to 40 per cent. of the cases, tuberculosis, where either the tubercle bacillus or various cocci have been found, anthrax, plague, and various localized infections due to staphylococci or streptococci. The fact that most observers have found traces of blood and albumin in the urine in association with the bacteria in these cases, and also in experimental injections of bacteria into the blood, suggests that in all probability the bloodvessels of the glomeruli undergo certain pathological changes before the bacteria can penetrate them. Nevertheless, according to Orth and Baumgarten the kidneys are permeable when lesions cannot be made out by microscopic examination, while Biedl and Kraus have shown that after the injection into the blood of various bacteria, within a few moments these same bacteria may be found in the urine without blood or albumin. It would seem probable, however, that in the majority of cases the glomerular bloodvessels would show slight changes, although in all probability in many cases these may be entirely recovered from within a comparatively short period.

In the vast majority of cases of bacteriuria the source of the bacteria is undoubtedly the gastro-intestinal tract, for it has been shown that even a slightly altered intestinal mucous membrane is pervious to bacteria; as a rule, ordinary constipation is not enough to allow this permeability, but if it is prolonged or associated with lesions of the mucous membranes, even though very slight, bacteria may reach the blood or lymph streams, and be carried to the kidney or the bladder, as the case may be, setting up a bacteriuria either of renal or of vesical origin.

As to the bacteria found in bacteriuria, the colon bacillus is met with in the vast majority of cases, but other bacteria have been found, such as the typhoid bacillus, various streptococci and staphylococci, sarcina, *Bacillus lactis aërogenes*, and in rare cases even the *Bacillus proteus*. Whether the case remains a pure bacteriuria, or whether an infection of the kidney substance, renal pelvis, ureter, bladder, or urethra subsequently appears, depends upon the resistance of the patient and the various factors predisposing to infection already considered.

Conclusions.—There are certain other questions which should be touched upon. It is important to remember that the epithelium of this tract is extremely resistant to infection, and that in the vast majority of cases certain predisposing factors must be met with before inflammation is set up. As regards the various modes of entrance of infection in the different inflammations of the urinary tract, there are certain other points which should be mentioned. In the first place, it is highly probable that in men spontaneous infection of the bladder from the urethra does not take place, probably due to the internal sphincter, while in women it unquestionably may occur, although in the vast majority of cases instrumentation or some other condition which lowers the resisting power of the bladder precedes it. In the second place, it is perfectly possible for a regurgitant blood stream to carry bacteria from the urethra to the bladder, and even from the bladder to the kidney, although these methods of infection must be rare. In the third place, under very slight pathological conditions of the intestinal tract, bacteria, especially the colon bacillus, may penetrate the intestine and enter the blood and lymph streams, to be carried thence to the kidney and bladder. The question of whether the bacteria, once having reached the blood stream,

can penetrate the healthy kidney is still a matter of discussion, but the weight of evidence is in favor of the view that in the majority of cases some lesion of the kidney, probably of the glomerular epithelium, must be met with, although this may be extremely slight and easily recovered from.

Another thing not to be forgotten is that many authors, especially in the past, have given new names to bacteria, which in reality are but varieties of well-known species, while the undoubted tendency to-day is not to differentiate bacteria according to very slight and possibly transitory differences, but to realize that we may meet slight cultural differences, and that this does not necessarily mean that we are dealing with a new group.

As to the constitutional effects of pyelitis, cystitis, etc., these depend largely upon the amount of absorption, and this in turn is dependent on the extent of injury which the epithelial layers have undergone. Thus, in acute cystitis there is considerable absorption, because the superficial cells are rapidly destroyed and the absorption of the poisons formed is rendered easy; obviously, if anything prevents the free flow of urine from the renal pelvis or bladder, the chances of absorption are markedly increased. In chronic cystitis the constitutional symptoms are less, as a rule, because the covering of pus, mucus, etc., over the ulcerated surfaces usually renders absorption slight. As to the poisons which cause these constitutional effects, the only ones carefully studied have been those formed by the colon bacillus in its growth; indol and two ptomaines, putrescine, and cadaverine, have been described.

The use of the agglutination test in diagnosing these infections of the urinary tract has been used in a number of instances, although it must be remembered that when dealing with the same bacterium agglutination will only take place with an homologous strain. Of course, in all cases we may either use precipitation tests, the thread reaction, Pfeiffer's phenomenon, or the ordinary agglutination test. The bacteria in which one or several of these tests have been described in connection with urinary infections are the colon bacillus, typhoid bacillus, *Bacillus lactis aërogenes*, tubercle bacillus, proteus bacillus, and various streptococci and staphylococci.

Serumtherapy and treatment by vaccination have been used extremely rarely in the case of these infections, but it would seem that in certain cases, notably chronic cases of pyelitis and pyelonephritis, these methods of treatment should be more extensively tried.

CHAPTER XI.

PYOGENIC INFECTIONS OF THE KIDNEY, URETER, AND PERIRENAL TISSUES.

By THOMAS R. BROWN, M.D.

It seems well to consider in one chapter the various pyogenic infections of the kidney and its pelvis—pyelitis, pyelonephritis, suppurative nephritis, suppurative pyelonephritis, pyelonephrosis, pyonephrosis, abscess of the kidney, and empyema of the renal pelvis. In the first place, the etiological factors are very similar, the same bacteria may be the primary cause, and the same predisposing factors may prepare the soil; in the second place, it is very difficult to differentiate the various forms of inflammation, as they so often occur together, one often causing another and fusing imperceptibly into it, in fact, often being but stages of one and the same pathological process; while in the third place, any of these may arise by bacteria reaching the kidney or its pelvis by any one of the usual three routes—ascending or urogenous infection, metastatic, descending or hæmatogenous infection, or infection by continuity from some adjacent focus of inflammation.

Pyelitis signifies an inflammation of the renal pelvis and its calices; *pyelonephritis*, where with this there is associated an inflammation of the kidney substance itself; *suppurative pyelonephritis, pyelonephrosis*, or *surgical kidney*, a suppurative inflammation of the kidney and its pelvis, associated with miliary or with larger abscesses in the kidney substance, and usually due to an ascending infection from lower portions of the urinary tract; *suppurative nephritis*, an inflammation of the kidney substance, usually hæmatogenous, traumatic, or by contiguity with the formation of miliary abscesses; while if we have one or several abscesses of larger size, usually due to the confluence of miliary abscesses, the condition is known as *abscess of the kidney*. In all cases of suppuration of the kidney, especially in the ascending forms, in which there is constriction of the ureter or other obstruction to the flow of urine, due to calculus, new-growth, pressure upon the ureter, prostatic hypertrophy, etc., we get a *pyonephrosis*, if the condition lasts for any considerable period, in which there is stagnation of urine and pus in the renal pelvis and its calices, causing destructive changes in the renal parenchyma and its subsequent conversion in many cases into a pus-filled sac, pyonephrosis differing from pyelonephritis merely in the degree of distention met with. Küster speaks of this form of pyonephrosis as *empyema of the renal pelvis*, while according to this author it is best to confine the term pyonephrosis to the infected hydronephrosis, under which heading this special form of infection will be considered. In almost all cases in which the renal pelvis is diseased we meet with involvement of the ureter and its surrounding tissues, ureteritis and peri-ureteritis, leading frequently to subsequent constriction of the ureter and secondary pyo-

nephrosis, while in cases of inflammation of the kidney substance, especially those in which the cortex is most affected, we may have an inflammation of the tissues surrounding the kidney, perinephritis, epinephritis, and paranephritis. The pyelitis consecutive to inflammations of the kidney substance is of minor importance in the majority of cases, although, on the other hand, the renal inflammations which follow pyelitis are of very great significance, almost always being associated with far more serious symptoms and a much worse prognosis than the pyelitis itself. This division of the infections of the kidney along anatomical lines seems far more satisfactory than one based upon etiological factors, as, for instance, the variety of bacteria causing the infection or the various accessory etiological factors.

Historically, suppuration of the kidneys was recognized by many of the older physicians, even by Hippocrates and Galen, but although Aretaeus separated the acute from the chronic cases, Hoffman attempted to classify the different forms, and Rayer described pyelitis as a separate infection and recognized that it was possible for the inflammation to spread upward from the renal pelvis, or downward from the kidney substance, nevertheless, it was the work of Koch, Traube, Lister, Klebs, and others which gave to clinicians a proper conception of the various processes, although Virchow's earlier work on metastasis helped much in this recognition. It must not be forgotten that Pasteur himself suggested that the decomposition of urine was due to microörganisms.

It has only been in the last few years, however, that these diseases have received much attention, and the literature, especially that devoted to autopsy records, abounds in undiagnosed cases, regarded during life as cases of malaria, anæmia, appendicitis, gallstones, diseases of the bladder, etc., or even believed to have had no disease whatsoever. Kapsammer collected records of 20,770 autopsies from various Austrian hospitals, where the newer diagnostic methods were not employed, and found among these 750 cases of pyelitis and pyelonephritis, over two-thirds of which had not been suspected during the life of the patient. By careful examination many cases of pyelitis can be diagnosed and cured before the kidney substance is involved, many cases of infection of the kidney and its pelvis will be avoided by the prompt recognition and the appropriate treatment of the antecedent causes, surgical interference, if necessary, will be inaugurated early, instead of as a last hope, and the mortality figures will be correspondingly lowered. Many of these cases, especially the suppurative inflammations of the kidney substance itself, are in their very nature surgical, and yet in practically all it is the physician who sees them first, and it is his keenness or dulness of vision which will be the most potent factor in deciding the outcome.

Etiology.—To get a proper conception of the various inflammations of the kidney and its pelvis it is absolutely essential to understand the causative factors involved, both the primary causes and the accessory factors. Practically all forms of inflammation of the kidney are due to bacteria, but in many cases, probably the majority, other etiological factors must be present before infection occurs. In certain cases we may have a pyelitis or pyelonephritis due to various poisons and drugs, or to the toxins produced in various diseases. The bacteria may reach the kidney or its pelvis by an ascending infection from the bladder and ureter, by descending infection by the blood stream, by way of the lymphatics or by contiguity from neighboring organs or tissues or from other portions of the kidney itself, or directly

from without by means of penetrating wounds. Under normal conditions the kidney and its pelvis shows marked resistance to infection; thus, bacteria of various kinds have been injected into the circulating blood and into the bladder, but no infection has occurred in many cases unless some trauma or impediment to the flow of urine has been artificially produced. It is also well known that in the course of many infectious diseases bacteria may pass through the kidneys without producing any permanent lesion. According to some, Sherrington and others, the glomerular bloodvessels and epithelium must be injured before bacteria can pass through, and this is shown by the presence of a trace of albumin and a small amount of blood in the urine, although this injury may be purely transitory and easily repaired; while, according to Baumgarten, Orth, and others, the kidneys are permeable to bacteria when no lesions can be made out with the microscope and when there is a complete absence of albumin and red corpuscles in the urine. The normal urine itself possesses distinct bactericidal properties, this probably being due to the acid phosphates present. When the resistance of the kidney or its pelvis has been lowered, infection may occur, and we may have one or several of the forms of inflammation previously mentioned. In some cases there is a true renal bacteriuria, in which the urine becomes infected without involvement of the kidney, and contains many bacteria, usually colon bacilli, but no pus cells; although, if stasis of urine occurs, or the resistance of the kidney is lowered, pyelitis or a renal infection may arise. The degree of infection in the individual case depends unquestionably to a certain extent upon the number, virulence, and character of the invading bacteria and their mode of entrance, but far more in the majority of cases upon various accessory factors which make the kidney a *locus minoris resistentiæ*, be those causes local or general.

Bacteriology of Pyelitis, Pyelonephritis, and Suppurative Inflammations of the Kidney.—A great variety of bacteria has been found in these conditions, much the same flora, in fact, as that met with in cystitis, although the relative frequency of the different species is quite different. Among the organisms found may be mentioned *Staphylococcus pyogenes aureus* and *albus*, *Streptococcus pyogenes*, *Diplococcus ureæ liquefaciens*, a urea-decomposing white staphylococcus, pneumococcus, *Bacillus proteus vulgaris*, typhoid and colon bacilli, *Sarcina flava* and *alba*, diphtheria bacillus, gonococcus, influenza bacillus, and various rare bacteria, the microörganisms being usually found in pure culture, although occasionally a mixed infection is met with. In all cases in which the microscope reveals bacteria, but nothing grows on the ordinary media, one should make anaërobic cultures, or at least use special staining reactions, while in all cases in which there is any doubt as to the etiology, especially if associated with an acid urine, the tubercle bacillus should be carefully looked for. Lenhartz, in 80 cases of pyelitis and pyelonephritis, most of which developed during or after pregnancy, found the colon bacillus 66 times in pure culture, paratyphoid bacillus 3 times, *Bacillus lactis aërogenes* twice, *Bacillus proteus vulgaris* twice, and Friedländer's pneumobacillus once. Von Albeck in 92 cases of pyelitis and pyelonephritis in pregnant women found the colon bacillus 76 times in pure culture, and 3 times with pyogenic cocci, staphylococci alone 4 times, and streptocci alone 9 times.

Rovsing found that the bacteria in men and in women differed somewhat: thus, in 18 cases in women the colon bacillus was found 16 times in pure

culture, once with the *Streptococcus ureæ*, and the *Streptococcus pyogenes aureus* once in pure culture; in 14 cases in men the colon bacillus was found 5 times, *Staphylococcus pyogenes aureus* twice, *Staphylococcus pyogenes albus* twice, *Bacillus liquefaciens* once, *Bacillus longus liquefaciens* once, *Sarcina flava* once—all in pure culture—while in one case *Staphylococcus pyogenes albus* and *Streptococcus pyogenes* were found, in another *Bacillus proteus vulgaris* and staphylococcus. In a series of 14 cases, 13 women and 1 man, observed by the writer, in all of which both kidneys were catheterized separately, the colon bacillus was found 8 times, *Bacillus proteus vulgaris* 3 times, a white staphylococcus, which decomposed urea but did not liquefy gelatin, twice; while in one, a case of thirty years' standing, no growth occurred, the bacteria evidently having died out. In all cases the bacteria were found in pure culture. Practically all series show the marked preponderance of the colon bacillus, although the pus cocci and the *Bacillus proteus vulgaris* are also frequently met with, this preponderance of the colon bacillus being unquestionably more marked in women than in men. According to Küster, the colon bacillus is the cause of the infection in at least one-third of the cases of suppurative nephritis, while Guyon and many others have stated that in their experience the colon bacillus is the commonest cause of all the infections of the urinary tract. As to the bacteriology of bacteriuria, although the colon bacillus is present in the vast majority of cases, *Bacillus lactis aërogenes*, *Staphylococcus pyogenes aureus* and *albus*, *Streptococcus pyogenes*, *Bacillus typhosus*, sarcina, and even *Bacillus proteus vulgaris*, have also been described. That the organs and urine of absolutely normal individuals are free from bacteria has the weight of authority, and thus, at the present time at least, it is not fair to assume that we may have autogenous infections of the kidney. Whether the gonococcus of itself can cause infection of the kidney is still under discussion, although it is difficult to explain certain cases on other grounds. Certainly its virulence is slight, and when the predisposing causes are removed a rapid cure occurs in the majority of cases.

Paths of Entry of the Bacteria.—There are a number of interesting and important points involved in considering the various paths of infection in these inflammations of the kidney and its pelvis. In each case we must determine whether the infection is hæmatogenous, urogenous, by contiguity, or by the medium of a penetrating wound. *Hæmatogenous* or *metastatic* infection may occur in any condition in which bacteria may get into the circulating blood, and thus reach the chief eliminatory organ of the body, the kidney; if these organs are healthy, the bacteria may pass through, doing no, or at least only transitory, harm, while if their resistance is lowered, whatever be the cause, there is a strong probability of inflammatory changes being set up in some portion of the organ. In regard to the commonest cause of renal infection, the colon bacillus, it has been very definitely shown by Posner, Lewin, and others that a pathological intestinal wall is pervious to bacteria, and that although ordinary constipation (from one and a half to two days) is not sufficient, longer constipation or surprisingly slight lesions of the mucous membranes allow the bacteria to enter the circulating blood; it has also been shown that the virulence of this bacillus is markedly increased in diarrhœa and other intestinal diseases, and this probably explains why in some cases it does no harm in its transit, while in others it may produce all grades of infection from a simple bacteriuria to a suppurative pyelonephritis of the most severe type.

The *urogenous* or *ascending* infection is peculiarly interesting for many reasons, especially because infection of the kidney so commonly follows that of the bladder, although there is still some question as to exactly how this occurs. The commonest cause of cystitis unquestionably is instrumentation, the catheter or other instrument often producing trauma, and introducing bacteria if the technique is faulty, while a study of the bacterial flora of the urethra shows that it is quite possible for cystitis to arise from that source; in men it is improbable that spontaneous infection of the bladder from the urethra may occur, but in women spontaneous infection from this source is undoubtedly met with.

It is a moot question whether Petit's old view that under normal circumstances no escape of the urine from the bladder into the ureters is possible because of the oblique course of the latter in the vesical musculature is supported by the facts. Lewin and Goldschmidt showed that this is not so in the case of rabbits, while Guyon and Courtade demonstrated that this reflux is far less likely to occur in dogs in which the bladder muscle is stronger. Sampson and Young found that considerable distention of the bladder in dogs, or in the cadaver, was possible without any fluid entering the ureter. Although Kelly showed a reflux of air from bladder to ureter, nevertheless, it is highly probable that in the vast majority of cases in health no reflux of fluid occurs even with considerable distention. In case of disease, however, such a reflux undoubtedly does occur, while as regards the various ways in which infection may reach the kidney after cystitis, this is discussed at length in Sampson's admirable monograph on the subject. After first calling attention to the mechanism by which the reflux is prevented under normal conditions by the structure of the ureters, although cases have been reported which seem to be exceptions, he then showed that bacteria may be carried from the bladder to the kidney by the general circulation, the vesico-ovario-renal anastomosis, the bloodvessels of the ureter (all these being examples of hæmatogenous infection), the lymphatics, or by the lumen of the ureter, which may occur in injuries of the intravesical portion, by extension of the inflammatory process, from the bladder along the lumen of the ureter, or through its wall—this being the commonest way, by the bacteria travelling up the ureter. This is obviously favored by anything which interferes with the free flow of urine, or by a reflux of urine from the bladder into the ureters which may be due to intravesical pressure, reverse peristalsis, or by suction of air into the ureters, as when patients are examined in the knee-chest position, "this reflux of urine being considered an etiological factor in the causation and maintenance of renal infection only when the intravesical portion of the ureter is diseased, or when some ureteral abnormality exists." Bond suggests that there may also be a regurgitant mucous stream which may aid somewhat in these ascending infections.

We may unquestionably have *direct transmission* of bacteria by way of lymphatics from the colon to the kidney, especially on the right side, where the two organs are in such close proximity, and this is peculiarly liable to occur in cases of nephroptosis.

Whether urogenous or hæmatogenous infections of the kidneys are most common is undecided; it seems unquestionable that when the renal pelvis is affected first the infection is more likely to be urogenous, although it is possible to have an uncomplicated pyelitis of hæmatogenous origin, while, in inflammations beginning in the kidney substance itself, hæmatogenous

infection is more common. In the series of 14 cases of pyelitis and pyelonephritis the infection was urogenous in 7 cases, hæmatogenous in 6, and by contiguity in one.

Accessory Etiological Factors.—While bacteria are always the primary cause except in those rare cases in which inflammatory changes are produced by various drugs, poisons, and toxins produced in the course of various diseases, nevertheless, in most cases other factors are involved without which the infection would not take place; although in the case of renal infections it is far more difficult to determine these predisposing causes than in the case of infections of the bladder. The importance of these accessory factors has been shown experimentally as well as clinically, although in the case of certain bacteria, especially if very virulent, if present in very large numbers, or if they have the power to decompose urea, thus producing substances irritating to the renal pelvis, infection may occur with no adjuvant causes.

Most of these accessory factors act either by lessening the general strength of the patient, by lowering the resistance of the kidney, by trauma, or by causing retention and stasis of the urine. Both clinically and experimentally the importance of this last factor has been determined, and stricture and encroachment upon the lumen of any portion of the urinary tract are among the most potent predisposing factors to the development of infection.

Among the accessory factors may be mentioned: Various *general* and *local infections*, such as pyæmia, septicæmia, ulcerative endocarditis, tuberculosis, pneumonia, tonsillar abscess, and many other infections, which not only lower the resistance of the patient, but also often furnish the infecting bacteria. It is even possible that in some of these cases a pyelitis may be produced by the toxins formed during the course of the disease, though in the great majority of instances the effect of these toxins is to lower the resistance of the kidney and to prepare it for the invading bacteria. In certain severe general infections we may get croupous, gangrenous, diphtheritic, and hemorrhagic pyelitis and pyelonephritis, although in most cases of infectious disease when pyelitis is present it is of the catarrhal variety. Marked *constipation* and *gastro-intestinal disease* may allow the bacteria to reach the kidneys either by the general circulation or by the lymphatics, while a distended colon may also easily compress the ureter and tend to produce urinary stasis. Other factors are *calculus*, although stone is more likely to be caused by pyelitis than the reverse; *diseases of the kidney*, such as the various forms of nephritis; *cystitis*, this in older people being almost always associated with retention, and if long continued almost always leading to pyelitis or pyelonephritis; *stricture of the ureter* or of the *urethra*, *narrow urinary meatus*, and *phimosis*, these causing retention of urine, and the two former frequently causing not only pyelitis and pyelonephritis, but also pyonephrosis or empyema of the renal pelvis; *wounds* of the kidney or its pelvis; *trauma*, frequently associated with small hemorrhages or tears in the kidney substance, or in the perinephric tissues; *chronic passive congestion;* some *near-by focus of inflammation*, such as acute appendicitis, pelvic peritonitis, etc.; *nephroptosis*, or floating kidney, unquestionably of importance, as the associated congestion and the slight degree of hydronephrosis met with in this condition lowers the organ's resistance, while stasis of the urine frequently follows kinking of the ureter; *hypertrophy of the prostate*, producing urinary stasis, and also often associated with various forms

of renal degeneration; the pressure of *tumors, inflammatory exudates, the pregnant uterus,* and possibly the *distended colon* upon the ureter, and the constriction of the ureter, due to *adhesions,* or consecutive to *ureteritis* and *peri-ureteritis; anæmia, unhygienic mode of life,* or *malnutrition, intercurrent disease,* or anything which may lower the general resistance; various *parasites,* such as actinomyces, which may of itself cause pyelitis, *Eustrongylus gigas,* filaria, echinococcus, bilharzia. *Tuberculosis of the kidney* is sometimes followed by secondary infection with one of the pyogenic bacteria, as also *paralysis of the bladder* from injury or disease of the spinal cord, etc. *Gonorrhœa* probably sometimes causes infection of the kidney, but is more often followed by a secondary infection due to other bacteria. The use of *instruments* may not only produce trauma, but also introduce bacteria. *Holding urine for a long period of time voluntarily* may be a cause. *Injuries* to the *rectum* or the mucous membrane of any portion of the *gastro-intestinal tract* may allow bacteria to enter the blood stream, and *cold,* possibly by lowering the resistance of the kidney, has been mentioned, although it is questionable whether this is really a contributory cause.

In any of these cases associated with a marked obstruction to a free flow of urine, unless this is removed within a short space of time, dilatation of all portions of the tract above the obstruction will occur, and an empyema of the renal pelvis results, or a pyonephrosis, if there is a coincident infection with injury and ultimate destruction of the renal tissue, unless relief, usually surgical, is obtained. This pyonephrosis is very frequent in pregnant and puerperal women, and is obviously more likely to occur in urogenous infections.

In the metastatic forms of renal infection the disease is usually bilateral, while in the cases due to trauma or to infection by contiguity, unilateral is the rule. In ascending or urogenous infections it is far more often unilateral. In our series of 14 cases of pyelitis and pyelonephritis, 7 of which were urogenous, 6 hæmatogenous, and 1 by contiguity, 13 were unilateral, 1 bilateral, and of the unilateral the right side was affected in 8, the left side in 5 cases. Other series give a far greater relative frequency of involvement of the right side than the left; the proximity of the right kidney to the colon and its tendency to descend may have something to do with this increased susceptibility. In all cases, if the infection has lasted for a long period, there is a tendency for the other kidney to become infected usually by way of the bladder, although in some cases it is remarkable how long one kidney may remain intact with advanced disease of the other, and even with cystitis. In the suppurative inflammations, which come to the surgeon, bilateral infection is more common than unilateral.

As to *age,* pyelitis and pyelonephritis are met with in children, even in very young infants to a considerable extent, although this has only been recently recognized, and even now in the majority of cases the proper diagnosis is not made; girls are more frequently affected than boys. In the aged the condition is common, due to the prevalence of many of the accessory factors mentioned above. The common years are between twenty and fifty, that is, the time when urethral troubles are most common in men, genital troubles in women, while it is also common in later life in men due to the tendency to enlargement of the prostate, and associated cystitis with retention. Senator has found that pyelitis and pyelonephritis are slightly more common in males, but the writer's experience has been the reverse.

Infections of the kidney and of its pelvis in *pregnancy* are of great importance. Von Albeck, in 7648 cases in Meyer's clinic, found pyuria in 392, and in 52 of these, that is, 14 per cent., there were signs which pointed to pyelitis or pyelonephritis. Lohlein and Olshausen have shown that the ureters are always dilated in women dying in labor, the dilatation being above the superior strait. Opitz has observed 84 cases during pregnancy and the puerperium, while Swift, who collected 41 cases, found that the right side was involved 37 times, the left side 4 times, and that of the 29 women in which the information was obtained, 15 were primiparous, 14 multiparous.

Pathological Anatomy.—**Pyelitis.**—The typical pyelitis is that met with in ascending or urogenous infections, while that consecutive to renal inflammation is not likely to be so severe or to show such marked pathological changes. In ascending pyelitis the pelvis of the kidney shows a most variable picture, according to the type of infection, its duration, its virulence, and with what accessory factors it is associated. The pelvis may not be dilated at all, may be slightly or moderately so, or if a constriction or obstruction occurs below the pelvis, if persisting for some time, there may be an extreme grade of distention. The urine in mild acute cases may be slightly cloudy, the cloud consisting of pus cells, mucus, a few epithelial cells, red blood cells and bacteria, usually not offensive if the bacteria do not decompose urea, but of ammoniacal or offensive odor, with a much thicker deposit, consisting in addition to the elements mentioned above of phosphates and oxalates of calcium and magnesium and a larger amount of mucus, if the infection be due to a urea-decomposing microörganism. The condition is usually unilateral, and even when the bladder is the primary source of infection it is surprising for how long a time in many cases one kidney alone may be affected. The exact cause of this is usually difficult to determine, although it is probably some local condition of the affected kidney which tends to lower its resistance; if the pelves of both kidneys are affected one is usually far more so than the other.

Acute catarrhal pyelitis gives the typical picture of an acute inflammation; the mucous membrane is congested, swollen, and hyperæmic, while on its surface may be seen red blood cells, pus cells, a few desquamated epithelial cells, mucus and bacteria in greater or less amounts, phosphate and oxalate crystals if the urine has been rendered alkaline, and even bits of calculus, if that happens to be the predisposing cause. The bacteria are often agglutinated masses, and these may be the nucleus around which a stone may form, although this is almost exclusively confined to the alkaline infections. Occasionally the blood is present in larger amount, due to trauma, the effect of certain toxines, to some peculiarity of the blood, or to an increased permeability of the bloodvessel wall; we may have ecchymoses and punctiform hemorrhages in the mucous membrane, and the fluid in the pelvis may be markedly bloody (hemorrhagic pyelitis). The submucous tissue is frequently involved, and may be swollen, œdematous, infiltrated, or hyperæmic. In the most intense forms portions of the mucous membrane may become ulcerated, necrotic, or gangrenous, while the rest of the mucous membrane is very red, swollen, and infiltrated, with marked inflammatory changes in the submucous tissue. Ulceration and necrosis of the mucous membrane are by no means so common in the acute as in the chronic forms of pyelitis, although in both they are more likely to occur when the infecting microörganisms have the power to decompose urea.

Chronic Pyelitis.—In this the picture is quite different; the mucous membrane is brownish or grayish-red in color, discolored spots frequently mark the remains of old hemorrhages, the mucous membrane is frequently pigmented and practically always markedly thickened, while the veins are enlarged and tortuous. The covering of the mucous membrane is markedly dependent upon the nature of the infection, and especially upon whether the urine is acid or alkaline. In acid infections the mucous membrane is covered with a layer, often quite thin, and very thick only in a small proportion of the cases, consisting of mucus, epithelial cells, pus cells, usually a few red blood cells, many bacteria often in clumps, and sometimes deposits of crystals of uric acid and urates, while in the case of the alkaline infections the coating is much thicker, as a rule, usually mucopurulent, with a foul odor, with phosphate and oxalate crystals embedded in it. The submucosa and often the entire wall of the pelvis are œdematous, or infiltrated with serum, pus, and bacteria. The contents of the pelvis may, even in chronic cases, especially those due to the colon bacillus, be simply a slightly cloudy fluid with no offensive odor, but in severe cases, especially of alkaline infections, the contents consist of a milky or a thick, purulent fluid, usually foul in odor, which sometimes contains mortar-like or putty-like masses, due to the inspissation and calcification of the pus. Ulceration is much more common than in acute pyelitis, and this is peculiarly so in those cases in which the urine shows ammoniacal decomposition. The ulcers are often very deep, and may in rare instances even perforate into the neighboring organs and tissues, especially the pararenal fat, leading to burrowing abscesses which may discharge externally or into a neighboring viscus, the fistulæ usually being very persistent. The mucous membrane may be thinner, or may show definite scars, which are the remains of old, healed ulcers.

Various forms have been described; thus, we have *gangrenous pyelitis*, not uncommon in chronic cases with marked ammoniacal decomposition of the urine, or in certain very intense infections; *cystic pyelitis*, in which small cysts, sometimes even microscopic in size, are found in the mucous membrane, filled with serum or gelatinous material, and sometimes associated with a similar condition of the ureteral mucous membrane—cystic ureteritis; cases in which the mucous membrane may be converted into shining, white scales, due to cholesteatomatous changes, while occasionally we may also get cartilaginous and calcific changes in the mucous membrane; *granular pyelitis*, in which solid granules resembling lymphoid nodules project from the surface of the mucous membrane into the cavity of the renal pelvis; *pseudomembranous pyelitis*, in which there are large shreds made up of fibrin, pus cells, and bacteria, which are sometimes discharged in the urine, and *fibrinous*, *croupous*, or *diphtheritic pyelitis.*

In cases of pyelitis consecutive to suppurative nephritis the pelvis is less likely to be seriously involved than in ascending infections, while in the latter case all stages of the cysto-uretero-pyelonephritis may be of marked severity. The substances produced by the ammoniacal decomposition of the urine are peculiarly destructive to the mucous membrane, and it is consequently in this class of cases that the most severe forms of pyelitis are found.

The corresponding *ureter* is usually involved in cases of ascending pyelitis, although in rare instances it may be entirely normal, although the bladder below and the renal pelvis above are markedly diseased. It is often affected along its entire course, while especially important are the changes about

the ureteral openings into the bladder; the orifice may be dilated and surrounded by a markedly congested mucous membrane, or it may have a punched-out appearance, with induration and congestion of the surrounding tissues, very suggestive of an ascending infection according to some, or it may be dilated, with dark-red mucous membrane between the lips and deep injection of the surface along the line of the ureter, significant of descending ureteritis, according to other observers. While these descriptions are unquestionably too schematic, nevertheless, a diseased condition of the mouth of the ureter is one of the most important diagnostic signs of renal infection. The mucous membrane of the ureter may be chiefly affected (*internal ureteritis*), or the surrounding connective and fatty tissue may also be involved (*external ureteritis* or *peri-ureteritis*). Consecutive to these the ureter is dilated in some places, constricted in others, with marked thickening of the walls if peri-ureteritis is present, in which case it is also often adherent to the surrounding tissues, while in some cases complete closure of the lumen may be found. The changes in the ureteral mucous membrane are of the same character as those in the mucous membrane of the renal pelvis. The changes in the ureter are much more common in ascending infections, although frequently met with in the descending type of disease; often in the latter case only the upper portion of the ureter is involved.

If there is obstruction in the ureter, or even in the urethra, we will get stasis of urine, and first distention of the pelvis, then of the calices, the papillæ becoming flattened and showing atrophic changes; as the process advances, the pelvis becomes more and more dilated at the expense of the renal tissue, until finally, if the obstruction is not removed, the entire kidney may be destroyed and converted into a large pus sac—and thus we may get varying grades of *pyonephrosis* or *empyema of the renal pelvis*, or even *hydronephrosis*, if the infection has died out, and the pus becomes absorbed. Sloughing of the calices, or even of the entire pelvis, may occur if the blood supply is markedly affected by the pressure of the fluid in the pelvis, or if the toxines are especially powerful. Foci of suppuration and inflammatory changes are met with in that part of the kidney not already destroyed, while frequently we have in one and the same picture the pathological changes characteristic of pyelitis, pyelonephritis, and pyonephrosis; the kidney tissue often shows areas of suppuration of greater or less size, and in these abscesses, which, as a rule, are filled with creamy or bloody pus, are found bits of necrotic tissue, phosphatic crystals, and material resembling sand and gravel. The distention of the calices is sometimes extremely marked, while the opening into the pelvis is often very narrow, and in some cases entirely closed. The kidney may be converted into one large abscess, or into a series of smaller abscesses separated by remains of the connective tissue, or may be converted into a fatty mass, often still containing a few pus cavities. The pus may become inspissated, calcified, or converted into a serous fluid by absorption. If the process extends through the kidney we may find inflammation of the capsule both fibrous and fatty, sometimes associated with abscess formation. The gradual dilatation of the pelvis and the calices, with papillary flattening, and subsequent atrophy and destruction of the kidney substance, the medulla being affected first and the cortex afterward, is peculiar to ascending pyonephrosis, while in the descending form the ureters are less likely to be affected and the cortex shows earlier

changes; in both cases the vessels in the pedicle are often of surprisingly small size.

Besides the pressure changes, the kidney may be markedly involved by an extension of the infection, and we may get a chronic interstitial nephritis, suppurative pyelonephritis, the pyonephritic changes just described, or abscess of the kidney. If the pyelitis is not associated with involvement of the kidney, there is usually no hypertrophy of the other organ, while such a compensatory change, if it does occur, suggests very strongly that the renal substance has become involved in the inflammatory process.

Ascending Pyelonephritis.—In certain cases it is surprising for how long a period of time the pyelitis may exist without involving the kidney substance itself; on the other hand, quite early in some cases, and in the majority of cases after a certain length of time, such involvement does occur. The bacteria usually invade the collecting and the uriniferous tubules, and the inflammation usually starts from these as a centre; bacteria may penetrate into the lymph spaces and interstitial tissue, and we may find scattered throughout the kidney, especially the medulla, although the cortex is also often involved, little areas of suppuration, which subsequently coalesce into abscesses of greater size with associated destruction of the surrounding parenchyma. Frequently, as an evidence of the extension of the infection, grayish lines are seen radiating from the points of the papillæ through the medulla, and sometimes even through the cortex; microscopically these are made up of masses of pus cells and bacteria; in the early stages red spots and lines are seen representing the hyperæmic stage of inflammation. The kidney is usually larger than normal, and is often soft, while if the process is extensive we find abscesses of various size, usually with a fairly thick surrounding sac and in which septa are sometimes seen. These abscesses may become encapsulated, or absorbed with subsequent contraction of the kidney, may become cyst-like in nature, may undergo calcific changes, or the pus may become thickened and somewhat changed, so that the abscesses are represented by thick, putty-like masses. Microscopically the affected tubular epithelium shows the usual inflammatory changes, becoming turbid and swollen, and finally disintegrating; fatty changes may occur, and sometimes proliferation takes place. We may see masses of bacteria in the collecting and uriniferous tubules, the lymph spaces, the interstitial tissue, and even throughout the kidney substance according to the duration and character of the infection. In the early stages, especially in the medulla and about the glomeruli, we find areas infiltrated with pus cells, surrounding a mass of bacteria, and when these areas soften we find miliary abscesses, which in turn may coalesce, forming abscesses of greater and greater size. In all cases of ascending pyelonephritis the medullary portion of the kidney is usually affected earlier than the cortical, and to a greater extent.

Chronic interstitial nephritis is a quite frequent sequel of pyelitis, the interstitial inflammation secondary to the infection of the renal pelvis leading finally to contraction of the kidney. The connective tissue proliferation is seen as much in the medulla as in the cortex, while macroscopically the kidney is small and thickened, the capsule, as a rule, not adherent, the parenchyma diminished, and the renal pelvis and often also the upper portion of the ureter dilated.

It is very common to meet many of these pathological conditions in the same case; distention of the renal pelvis and calices, abscesses in the kidney

of greater or less size, destructive changes in the renal parenchyma, proliferation with subsequent contraction of the interstitial connective tissue, pyonephrosis or empyema of the renal pelvis, interstitial and parenchymatous nephritis, processes tending toward healing, ureteritis and peri-ureteritis, paranephritis and perinephritis may occur in various combinations, although usually one especial process dominates the individual case. If suppuration has been present for a considerable period of time, we may have amyloid degeneration of the kidneys or of other organs, while in some cases the renal suppuration may be the starting point of pyæmia or septicæmia, and in addition we may have extension of the suppuration, either by contiguity or metastasis. Compensatory hypertrophy of the intact kidney, if the condition is unilateral, or of the unaffected portions of the kidney is likely to occur when the process has been associated with a certain amount of destruction of the kidney substance, while in some cases cardiac hypertrophy may also occur.

Hæmatogenous Infections.—In these the condition is far more likely to be bilateral than unilateral. We may find a pure pyelitis with practically the picture already described due to metastasis, but in the majority of cases the pyelitis met with in descending infections either arises simultaneously with the infection of the kidney itself, or is a direct sequel to it; in some cases the cortex and pelvis may be involved at the same time, while in others the process is localized first, and often for a considerable time in the kidney substance alone. Areas of hyperæmia are followed by suppuration and abscess formation, with masses of bacteria as the causative factor, but unlike the ascending infections the bacteria are more likely to be found in and about the bloodvessels, and the cortex is more likely to be primarily involved. In the infected area the epithelial cells show the usual inflammatory and degenerative changes, while bacteria, besides being seen in the bloodvessels, may be found in the interstitial connective tissue, setting up degenerative and proliferative changes and the formation of areas of suppuration which subsequently soften and become abscesses, these, in turn, frequently coalescing into abscesses of large size. The organ is usually swollen and of a rather mottled appearance, the little abscesses being easily seen through the capsule, which is peculiarly liable to become adherent. Due to the distribution of the bloodvessels we sometimes find that the areas affected become wedge-shaped, with the point directed toward the centre of the organ. When the process becomes chronic the abscesses, more likely to be found in the cortex, become larger and give a rough appearance to the surface of the kidney, while the changes in the medulla, although similar in nature, are neither so marked nor distributed with such regularity as in the case of the cortex. It is not uncommon to find bacterial emboli in the bloodvessels.

The abscesses in hæmatogenous infections are not likely to be as large as those of urogenous origin, but about them are seen the same inflammatory and atrophic changes. The abscesses, whether small or large, contain pus cells, red blood cells, bacteria, shreds of necrotic tissues, epithelial cells, showing various stages of degeneration, and may undergo absorption, calcification, or the other changes before described. If these abscesses are found in the neighborhood of the tubules, rupture may occur and the urine show a sudden and marked change in composition, often of great diagnostic importance. By this form of invasion, by direct extension, or by a

simultaneous infection through the bloodvessels, an associated or secondary pyelitis may arise.

As in the case of the ascending infections, the picture is likely to be a diversified one. Suppurative nephritis with the formation of kidney abscesses, interstitial and parenchymatous nephritis, pressure atrophy of the kidney, pyelitis, and ureteritis may often all be found in association, while involvement of the fibrous and fatty capsule is peculiarly likely to occur in descending infections, and other organs and tissues may be involved by contiguity or metastasis. If the causative factor is removed, an attempt at healing may occur, the abscesses may become encapsulated, or may undergo calcific or fatty changes. In all cases of unilateral inflammation, hypertrophy of the healthy kidney occurs, if the process has lasted any length of time, while in the case of involvement of both kidneys regenerative changes are found in the portions not affected by the disease. There is always in the unilateral cases a tendency for the other kidney to be affected, usually by way of the bladder.

Traumatic Infections.—In these cases we meet, according to the nature of the wound and the character of the invading microörganism, either small, localized foci of inflammation surrounding the hemorrhages due to the injury, or larger abscesses filled with pus, necrotic tissue, bacteria, etc., with marked destruction of the renal tissue; in the most severe types the entire organ may be destroyed, and the suppurative process may involve the renal pelvis, the fibrous and fatty capsules, and the retrorenal fat. The small, localized areas of suppuration may subsequently coalesce into abscesses of larger size, and about them the epithelial cells and interstitial connective tissue undergo similar changes to those described in pyelonephritis. The abscesses may burrow along fistulous paths, and reach the surface of some neighboring or even far distant viscus, the frequently associated involvement of the paranephric fat rendering this comparatively easy; the abscesses may rupture directly into the renal pelvis, causing a pyelitis, they may give rise to pyæmia or septicæmia, or they may set up metastatic inflammations in other organs, a possibility in the case of all forms of renal suppuration.

Infections by Contiguity.—In these the picture is much the same as the preceding one except that the extravasations of blood, the laceration of the kidney substance, and the other signs peculiar to the injury are lacking. As regards healing, by far the most favorable prognosis is found in traumatic infections of mild extent.

In any form of renal inflammation, whenever the inflammatory process reaches the surface of the kidney, perinephritis with adhesions between the kidney and its capsule is likely to occur, and from this source the inflammation frequently spreads to the fatty capsule, and the retrorenal fat.

Symptoms.—Many cases of pyogenic infection of the kidney and of its pelvis are peculiarly devoid of characteristic symptoms, although careful examination, especially of the urine, should throw light on a considerable proportion. The symptoms may be practically wanting altogether, or they may be so vague and indefinite as to be regarded as due to some other cause. It is a good rule that in every case of doubtful etiology, especially if associated with slight pain or sensitiveness in the back or either flank, with vague febrile symptoms, or with constitutional disturbances without definite cause, a careful urine examination should be made, with the use of the cystoscope, and the ureteral catheter, if the urinary findings seem to warrant it. Urinary

examinations are peculiarly valuable in the case of infants and children when the symptoms are especially vague and confusing, and in whom the vast majority of cases unquestionably go unrecognized.

In many cases of renal infection the onset is very insidious, the pain never acute, the fever never high, while in others the disease may be ushered in by most violent symptoms, severe pain, chills, and high temperature, severe constitutional disturbances, etc.; in all cases the symptoms are very dependent upon the primary disease, the symptoms of which in many cases may absolutely dominate the picture, as, for example, in many cases of pyelitis during the acute infectious diseases, pyelitis secondary to cystitis, vesical paralysis, gonorrhœa, prostatic hypertrophy, etc., and in many cases of descending infection, especially when the kidney involvement is secondary to pyæmia, septicæmia, or ulcerative endocarditis. In pyelitis associated with calculus, and after various irritating drugs, the symptoms are more likely to be characteristic. Pyelitis may last for years with practically no symptoms, although, even in those of most chronic course, a careful history usually elicits some suggestive symptoms, such as slight soreness, occasional slight febrile attacks with no apparent cause, and slight urinary abnormalities.

In *acute pyelitis* we may have the usual symptoms of an acute inflammation, fever, chills, constitutional disturbances, etc., while in the *chronic form* acute exacerbations are frequently met with, the symptoms usually resembling those of an acute attack, while between the attacks the symptoms may have entirely disappeared or become very slight. It is not at all uncommon for the acute cases and the exacerbations of the chronic cases to be regarded as appendicitis, while mild types of the disease are frequently regarded as lumbago.

It is often most difficult to determine when a pyelitis goes over into a pyelonephritis, for even the latter process may last for years without any striking symptoms. Usually, however, involvement of the kidney substance is associated with a marked increase in the severity of the symptoms, the local and especially the constitutional, while if both kidneys are involved very grave symptoms may supervene. In acute pyelitis and pyelonephritis death may occur quickly, or the patient may gradually wear out, the terminal symptoms being sometimes due to general toxæmia, other times to uræmia or ammoniæmia; the symptoms may suddenly or gradually disappear and a cure take place, the acute may pass into a chronic inflammation, or the condition may be chronic in character from its incipiency.

In many cases of *suppurative nephritis* there is a complete absence of symptoms, the manifestations of the primary disease completely overshadowing the renal manifestations, this being especially so in the suppurative nephritis with metastatic miliary abscesses met with as a sequel to pyæmia, septicæmia, etc.; even the cystitis, which is secondary to this form of renal infection, often gives very mild symptoms. In the traumatic renal suppurations and those in which the kidney is suddenly affected by metastasis from some local focus of infection, the symptoms, as a rule, are more definite, while in those cases infected by direct extension from some adjoining focus, the symptoms of the primary disease are likely to predominate. In abscess sudden rupture may complicate the picture, the symptoms either becoming more or less severe, or even disappearing altogether, according to where the rupture occurs.

In *pyonephrosis* the clinical symptoms are most variable according to

the etiology; they may be very slight if drainage is good, while in this case, as in the case of all other renal suppurations, any condition which produces obstruction to the flow of urine usually causes a sudden exacerbation of symptoms.

During pregnancy and the puerperium we should always keep in mind the possibility of bladder and renal infections, and here as in other forms of pyelitis, pyelonephritis, and renal suppuration, the presence of leukocytosis sometimes aids in the diagnosis.

The main symptoms of the pyogenic infections of the kidney and its pelvis are changes in the urine, pain, swelling, and constitutional disturbances, and these will be considered in order.

Urine.—The changes in the urine are most important, but although the picture may be suggestive even in voided specimens, nevertheless it is essential to examine catheterized specimens, and, if necessary, even to obtain specimens from the kidneys separately by ureteral catheterization. In many of the cases the patients themselves have noted urinary symptoms, and pain, increased frequency, and other symptoms may call the patient's attention for the first time to the urinary tract, although obviously these symptoms may be entirely referable to the bladder. If ureteral catheterization is done, it is important to watch the rate of flow; normally this is drop by drop, while in cases of pyonephrosis and hydronephrosis and pyo-ureter and hydro-ureter the flow is in a steady stream until the ureter or pelvis is emptied, after which the flow is usually very sluggish. In all cases it is wise to make many examinations of the urine, both morning and evening specimens, for it is not at all uncommon in various infections for the urine to be absolutely normal for a considerable period, as, for example, after occlusion of the ureter on the diseased side by stone, mucus, blood, pus, etc. When the bladder is infected it is especially important to obtain separate specimens from each kidney, although it is necessary to be very careful so as not to introduce infection.

Anuria sometimes occurs in renal infections, as after trauma with reflex inhibition of the other kidney, here often preceded by transient hæmaturia, in cases of obstruction due to stone, fibrin, pus, mucus, bits of tissue, etc., when the other kidney is similarly affected, or in very severe infections in which either or both sides are involved, or only one involved but the function of the other reflexly suspended, or when one kidney has been removed and the remaining kidney is diseased.

Because of changes in the virulence of the infection and in the predisposing factors, the anuria or oliguria due to the causes just mentioned, the possibility of complications arising, as, for instance, the sudden rupturing of an abscess into the pelvis of the kidney or the ureter, the urinary picture is frequently changing, and these alternations in the character of the urine, in its pus and albumin content, in its reaction and specific gravity, in the amount voided in the unit of time, are of extreme importance in aiding us to reach a proper conception of the underlying process.

In *acute pyelitis* the *amount* is usually diminished, sometimes there is complete anuria due to the severity of the infection, the involvement of both kidneys, or to the stoppage of one ureter and the reflex inhibition of the other kidney. There is usually *increased frequency* of urination, sometimes with pain or burning, even when the bladder is not involved; the specific gravity is usually increased, the reaction is usually acid, but may be neutral

or alkaline, according to the peculiarities of the invading bacteria. In infections with colon and typhoid bacilli it is always acid; in fact, in certain cases its acidity is definitely increased; albumin is usually present, often in moderate amount, due partly to the pus and red blood cells present, partly to the effect of the fever and toxins. According to most observers, the amount of albumin in uncomplicated pyelitis, whether acute or chronic, can be entirely accounted for by the pus and blood; personal observations, on the other hand, have seemed to show that even when there is no involvement of the kidney the albumin is present in greater amount than can be thus accounted for, and this relatively greater quantity of albumin is a useful means of differentiating pyelitis from cystitis with the same grade of pyuria, Rosenfeld reaching the same conclusions; the involvement of the kidney usually produces an increase in the amount of albumin. Microscopically pus cells, red blood cells, epithelial cells, mucus, sometimes fibrin, and in all cases numbers of bacteria, sometimes actively motile, are found. In case of hemorrhagic pyelitis, red blood corpuscles are present in large amount; in a few cases a marked tendency of the pus cells to active pseudopodic movements is seen, probably due to the effect of the toxins upon them. If the bacteria cause alkaline decomposition of the urine, the odor may be ammoniacal and the mucopus thick and ropy, with phosphate and oxalate crystals embedded in it.

In *chronic pyelitis* and *ascending pyelonephritis* the urinary changes have been studied more carefully than in any other form of renal infection. The amount is usually increased, although oliguria, and occasionally anuria, are met with in the acute exacerbations; several liters are sometimes passed daily, while in personally observed cases the average amount was 2200 cc. Polyuria may be constant or intermittent, the latter being more common with oliguria during the acute exacerbations.

In *chronic pyelonephritis* the urine may be increased or normal in amount, as in pyelitis, although if both kidneys are involved oliguria is the rule. The specific gravity is usually low, varying with the amount passed, although high in the exacerbations. The color is usually light yellow, although it may be dark red in the exacerbations. The odor is usually slight unless in alkaline infections, when it is often ammoniacal, especially if the bladder is also involved; it may be very foul in gangrenous pyelitis. The reaction depends upon the variety of the bacteria; the pus cocci usually lessen the acidity, but generally slowly, so that the urine may be either less acid than usual, neutral, or sometimes alkaline. The reaction of the voided specimens in alkaline infections may be either acid, although, of course, less so than normal, or alkaline, according to the type of the infection and whether the bladder is also involved. Whenever the urine is alkaline it is always well to determine whether the patient is taking alkalies by mouth. The percentage of urea is usually low, due to the polyuria; the twenty-four-hour amount, however, is often normal, except when both kidneys are involved. *Albumin*, consisting of a mixture of serum albumin and nucleo-albumin, is always present; in pyelonephritis the amount of albumin is dependent upon the degree of renal involvement, although in many cases it is absolutely impossible to determine from the albumin, or, in fact, from any other urinary findings, whether we are dealing with a case of pyelitis or pyelonephritis.

It is important to determine the amount of the sediment, as by its increase

or decrease we can tell something about the course of the disease and the effect of treatment. Immediately after being passed, the urine is usually cloudy, due to bacteria and pus cells, and the sudden disappearance of this cloudiness is very suggestive of stoppage of the ureter on the diseased side. The sediment is usually thicker in alkaline infections, especially if the bladder is also involved, while rarely we can see bits of kidney substance or particles of stone, the latter sinking to the bottom as a fine black debris, especially in kidney washings from the ureteral catheter.

The microscopic examination is most important. *Pus cells* are practically always seen in greater or less amount, often in clumps, sometimes markedly degenerated, showing fatty changes, etc., as in alkaline infections, while according to some their crenations suggest a kidney origin, which view is probably wrong. The pus cells may be counted with the hæmatocytometer, which may aid in determining whether the condition is getting better or worse. Red blood cells are usually present in small amounts, except in those cases associated with stone, new-growth, or tuberculosis. The red blood cells and pus cells may appear as definite casts. *Bits of renal tissue*, although very rare, are important in showing kidney involvement. The long-tailed or caudate transitional cells in a tile-like arrangement, which used to be considered diagnostic of pyelitis, are in reality not so, as they are met with in the lower layers of the epithelium of the bladder and ureter; their predominance with absence of the characteristic flat cells from the bladder would be somewhat suggestive of pyelitis, although never diagnostic. *Bacteria* are always present, often in clumps, sometimes in casts, the latter especially in pyelonephritis. The various formed elements and especially the bacteria may be markedly increased during the acute exacerbations of the disease. *Hyaline, granular,* and *epithelial casts* are found in certain cases of pyelonephritis, but they are not at all constant, and casts from the prostate may prove confusing in this connection. Among other substances which have been found are casts of the renal pelvis, bits of necrotic tissue, bits of neoplasm, if this happens to be the primary cause of pyelitis, portions of calculus, cheesy moulds of the renal pelvis, casts of the ureter, and in alkaline infections, phosphate and oxalate crystals and amorphous phosphates; in acid infections sometimes uric acid crystals and amorphous urates.

In *suppurative nephritis and renal abscess* there is usually neither increased frequency nor pain on micturition; the urine may be normal as to its *amount* and *character*, as, for instance, when the process is localized in the cortex and not in close connection with the tubules, or in encapsulated abscess. The passage of *bits of renal tissue*, although very rare, is an important aid to diagnosis. In all cases in which both kidneys are considerably involved, or the kidney which is not affected is not functioning properly, the *quantity* is diminished; the urine may contain *blood* and *pus cells, renal epithelial cells,* all forms of *casts*, including pus and bacterial casts, if there is much involvement of the kidney tissue near the tubules. The sudden appearance of a large amount of pus is very suggestive of an abscess rupturing into the renal pelvis, and is often accompanied by marked improvement in the symptoms and a lessening in the swelling. In suppurative nephritis and descending pyelonephritis the *bladder* is not so likely to be markedly affected as in the ascending forms. In miliary metastatic abscesses of the kidney secondary to general infections the urine often shows neither pus cells nor red blood cells, and if present they are usually found in very small numbers;

a careful examination generally reveals bacteria, while the amount of urine is usually diminished, due to the primary process.

Traumatic nephritis often begins with a transient hæmaturia followed by anuria. The subsequent character of the urine depends on the site of the inflammation and its course; the urine may be absolutely unchanged, as when the abscess is discharging externally or is completely encapsulated, or we have the urinary picture of a suppurative nephritis or a pyelonephritis. Practically the same urinary findings, barring the initial hæmaturia and anuria, are seen in *infections by contiguity*. *Pyonephrosis*, if closed, may have normal urine, while if open there is always pyuria, although it may cease temporarily or permanently, as when obstruction occurs or the kidney becomes completely destroyed. The flow of urine through the ureteral catheter in pyonephrosis is very characteristic—a steady flow until the pelvis is emptied, and then a sluggish stream. In *bacteriuria* the urinary symptoms are usually nil, although occasionally we find increased frequency and some burning on micturition, possibly due to an excess of acid caused by the growth of the bacteria. In pure bacteriuria the urine contains no pus cells, but myriads of bacteria, usually colon bacilli.

In the urinary findings are by far the most important symptoms of renal infection, although even these may be most misleading; the urine may be normal, due to stoppage of flow from the diseased kidney, or because the process is not closely connected with the uriniferous tubules; the urinary findings of the cystitis so frequently associated with pyelitis and pyelonephritis may markedly complicate matters, and the pyuria may not arise from the urinary tract at all, but from some focus of suppuration elsewhere opening into the renal pelvis, ureter, or bladder, as appendicular abscess, pyosalpinx, etc.

Pain.—Pain, sensitiveness to pressure, or a feeling of pressure or fulness, is often the first symptom that suggests any renal trouble, and if present it is a most valuable sign, although frequently absent, as, for instance, in some cases of pyelitis and pyelonephritis, in metastatic miliary abscesses, in long encapsulated abscesses, and in certain cases of suppurative nephritis and pyonephrosis. In pyelitis and pyelonephritis there may be constant pain or sensitiveness to pressure, or these symptoms may only be present during acute exacerbations; in our series, pain, a feeling of pressure or weight, a girdle sensation, or sensitiveness to pressure was present in more than 75 per cent. of the cases, although in many instances slight and only elicited by careful questioning. Pain is usually more marked with stone, although in pyelitis alone the pain may be so severe, due to plugging of the ureter, that we may have a typical renal colic, which can only be differentiated from stone by the use of the *x*-rays, the wax-tipped catheter, or at operation. In *acute pyelitis* and in *exacerbations of the chronic form* the pain and sensitiveness are usually more marked, and sometimes very severe; although usually localized fairly well in the kidney region, it often radiates downward to the thigh, perineum, or genitalia, or upward to the stomach or shoulder, and it is usually increased on exertion. A sudden increase or re-appearance of the pain in the chronic form is very suggestive of stoppage of the ureter, while pronounced and persistent pain associated with chills and fever is frequently the sign of the formation of a renal abscess consecutive to pyelonephritis. Ureteral pain due to stone, stricture, etc., may be difficult to differentiate from renal pain.

In *pyonephrosis* about one-half the patients complain of more or less pain, a considerably larger proportion of pain on pressure, and many have a feeling of fulness or discomfort in the renal region, and here, as in practically all other renal infections, the presence of pain bears a close relationship as to whether the drainage of the kidney is good or not.

In *hæmatogenous suppurative nephritis* and *pyelonephritis* the pain is often rather diffuse at first, later being localized in the renal region, while, especially if associated with abscess, it may be very intense and markedly increased by pressure, movements, etc., sometimes muscle spasm even being present, although this is rare unless the perinephric and paranephric tissues are also affected. In the miliary metastatic abscesses met with in the course of various general infections, severe pain is rarely present, but there is usually a dull, heavy feeling with more or less sensitiveness to pressure, the latter being often quite marked.

In infants and young children the presence of colicky pain of doubtful origin, with drawing up of the legs, and screaming if the upright position is assumed, should make us suspicious of cystitis, pyelitis, or pyelonephritis, and should require an immediate urinary examination.

Swelling.—Swelling or tumor, if present, is of the utmost value, although its absence does not in the least rule out renal infection. If present at all, it is usually of slight extent, although rarely it may be marked, as in some cases of pyonephrosis, and in renal infections associated with perinephritis and paranephritis; in these latter instances the overlying skin may be markedly œdematous. On the other hand, the kidneys, especially the left, often lie so deeply that even if swollen they cannot be made out by palpation, while in many cases the swelling is so slight that it cannot be determined with certainty even if the kidney can be palpated.

In *acute pyelitis* the swelling is usually slight and often cannot be made out with certainty; in *chronic pyelitis* it is usually not demonstrable except during the acute exacerbations, when it may be quite marked; in *pyelonephritis* swelling may sometimes be made out, especially if there is obstruction to the flow of urine, although here we may even have contraction of the kidney due to regressive changes; in *pyonephrosis* the kidney can often be felt, especially, of course, if the drainage is not good, while in *purulent nephritis* with abscess formation the tumor, although rarely of large size, may usually be determined by careful palpation, although in the miliary metastatic abscesses of the kidney consecutive to general infection no swelling can be made out, as a rule; in cases of *infection by contiguity*, although swelling is often made out, it is difficult to differentiate it from the primary process; in some cases, however, this is possible by the characteristic shape and feeling. In some of the cases of renal infection a careful inspection may show some fulness in the affected flank, and in very rare cases of extreme swelling it may be noticeable on the anterior surface of the abdomen.

Constitutional Symptoms.—Constitutional symptoms are usually present at some time during the course of the disease, although often regarded as due to some other cause. Pyelitis and even pyelonephritis may last for years without any apparent constitutional disturbances, especially when the organism is not especially virulent, the urinary stasis slight, and the patient naturally vigorous; nevertheless, careful questioning will usually elicit some, if very slight, symptoms, loss of strength, slight digestive disturbances, mild febrile attacks, etc. Encapsulated renal abscess may give no

general symptoms, while in many cases of suppurative nephritis met with in the course of general infections, or due to contiguity from some neighboring focus of inflammation, the constitutional symptoms are in no way different from those of the primary disease. The constitutional effects depend to a great extent on the amount of absorption, and for that reason are always increased by any condition which obstructs the flow of urine. It has been shown that the poisons produced by certain bacteria have a marked effect upon the nervous system, and also can produce destructive changes in the gastro-intestinal mucous membrane. As these constitutional symptoms are seen in unilateral cases when the urine is normal as regards the amount of urea secreted, etc., they are probably due more to the toxins produced by the infection than to renal insufficiency.

The general symptoms are the usual ones met with in fever and toxæmia, although differing markedly in degree according to the virulence of the infection, the resisting power of the patient, the accessory factors present, the amount of urinary stasis, etc. The most common symptoms are chills, fever, and sweats, general physical depression, loss of weight and strength, and digestive disturbances.

In *acute pyelitis* the patient usually complains of extreme weakness, chills, fever, and often profuse sweats, complete loss of appetite, and localized pain, sometimes also pain and increased frequency of urination, even when cystitis is not associated with it. There is sometimes diarrhœa, while nausea and vomiting are quite common; the pulse is usually rapid and full. These symptoms last in their severity for only a few days, and then either disappear suddenly or gradually merge into those of the chronic form.

In *chronic pyelitis* the patient may have increased thirst due to the polyuria, appetite is usually diminished, dyspeptic disturbances frequent, and slight fever and diarrhœa are also met with, these symptoms varying markedly in different cases, and possibly being absent altogether; there may be a tendency to profuse sweating, sometimes although not always associated with exacerbations of the disease. Increased pulse tension and enlarged heart are not seen, as a rule, in pure pyelitis, while if the kidney is considerably involved the tension is usually high, and the heart occasionally hypertrophied; there are also sometimes uræmic manifestations and changes in the eye grounds. In the exacerbations the symptoms very closely resemble those of acute pyelitis.

If pyelonephritis should arise, the general symptoms are usually more severe, although not necessarily so; if the kidney is markedly involved in the inflammatory process, loss of weight, coated tongue, marked digestive disturbances, poor powers of resistance, and more or less fever are usually seen, the symptoms resembling to a considerable extent those of small contracted kidney. The more frequent these acute exacerbations of pyelitis and pyelonephritis, the more marked the constitutional symptoms and the more rapid the course of the disease.

Severe general symptoms are the rule in cases of *renal suppuration* secondary to trauma, by contiguity, or from some localized focus of inflammation by metastasis—high fever, chills, pain, loss of appetite, digestive disturbances, weakness, and in some cases a typhoid state with delirium and coma. True uræmia is rare, probably largely because this type of inflammation is usually unilateral, but in severe cases of alkaline infections, especially if retention is marked, ammoniæmia may occur. A high tension

pulse and less often cardiac hypertrophy are sometimes found where the renal involvement is considerable, and in most chronic cases anæmia and malnutrition are marked. In all cases of renal suppuration the symptoms are markedly aggravated by any condition which causes urinary stasis.

In the pyelitis and pyelonephritis of *pregnancy* the symptoms are most capricious, the highest fever and the most severe constitutional effects disappearing in some cases with great suddenness from no apparent cause, or simply due to rest in bed. In most cases, however, such an outcome does not occur, and we have the symptoms of a chronic pyelitis with very frequent exacerbations. In *children* restlessness, pallor, loss of appetite, and depression are often the only signs, and in these, as in adults, the symptoms of the disease may simulate those of typhoid fever, tuberculosis, epidemic influenza, or gastro-enteritis. The presence of chills and fever in infants is very suggestive of pyelitis.

The *fever* in renal infections is very variable; in the acute form and in the exacerbation of the chronic and in any conditions producing sudden stoppage of the flow of urine from the diseased organ, it is often quite high, sometimes constant, but more often remittent or intermittent, and often associated with chills and profuse sweats. Remittent fever with chills is usually met with in purulent renal inflammations, whether metastatic, traumatic, or by contiguity, while repeated chills with septic temperature are suggestive of an improperly drained abscess. In acute pyelitis the initial temperature may be high, reaching 104° or even 106°, although usually not so elevated; subsequently it may become remittent, intermittent, or disappear altogether. In ascending pyelonephritis fever is rarely absent, while in open pyonephrosis fever and apyrexia are present with about equal frequency.

In all forms of unilateral infection a sudden increase of the constitutional symptoms may be due to infection of the other kidney. In certain cases of chronic pyelitis, pyelonephritis, pyonephrosis and abscess, fever may be entirely lacking. Long-standing cases of renal inflammation or cases of great severity may give rise to pyæmia or septicæmia with their characteristic temperature charts, the patient dying either of the pyæmia or septicæmia itself, from amyloid degeneration, from some intercurrent disease, the rupture of an abscess into the peritoneal cavity, or by hemorrhage from some large necrosed vessel.

Diagnosis.—In the diagnosis of renal infections many questions suggest themselves: Are we dealing with a disease of the kidney or its pelvis; if so, of what nature? Is one or are both sides affected? If operation is under discussion, is the remaining kidney able to properly perform the renal functions?

In examining the urine it is most important, especially in women, to obtain a catheterized specimen, while if possible the ureteral catheter should also be used, so that we may examine separate specimens from the two kidneys. The most important element in the urine is the pus, but in addition to this the specific gravity, the reaction, and the amount of albumin should be determined and the sediment carefully examined for red blood cells, epithelial cells, mononuclear leukocytes, casts, bacteria, bits of renal tissue, bits of membrane, fragments of stone, various crystals, mucus, and parasites. Cultures should be made, while in some cases it is interesting, although not of special diagnostic importance, to test the bacteria obtained with the patient's

serum, using the agglutination, precipitation, thread, or Pfeiffer reaction; this has been done successfully in the case of the colon, proteus, and typhoid bacilli, *Bacillus lactis aërogenes*, and streptococcus. The pus cells and the bacteria may be counted, and their increase or decrease is of some help to us in determining whether or not improvement is really taking place.

Whenever we wish to determine whether the kidney is involved, and if so, to what extent, especially if operation is under consideration, we should make use of the so-called functional tests, which, though not certain, are at least helpful in many cases, the tests, of course, being made with the urines from the two kidneys obtained simultaneously. The functional integrity cannot be determined definitely, it is true, by these tests, as the time is too short, and other factors play a role, such as the reflex inhibition of a normal kidney by a diseased organ, but if positive they are of unquestionable value. The most important functional tests are the urea determination, color tests, cryoscopy of the urine, determination of the specific gravity, phloridzin and dilution tests, the figures in all cases being lower in the diseased kidney; although there may be considerable question as to their value, they have, nevertheless, one great merit—they demonstrate the presence of both kidneys, a most important fact in cases in which operation is under discussion.

A cystoscopic examination of the bladder should be made to determine whether cystitis is present, and to carefully inspect the ureteral orifices, for by their appearance we may determine with a high degree of probability in many cases whether or not the renal pelvis or kidney is diseased, and we may also notice the character of the urine flowing from the two openings and determine whether there is any ureteral stoppage; in cases where they are difficult to find we may give indigo carmine or methylene blue hypodermically, and the flow of colored urine will easily show us the ureteral mouths. In addition, by the use of the ureteral catheter we can determine the presence of stricture, and even measure very accurately its degree; we may measure the capacity of the renal pelvis and determine whether it is distended or not, while by using wax on the catheter tip we may determine the presence of stone. The use of urine segregators or separators has not found much favor, as the results are too inaccurate. In infants it is often difficult to obtain the urine for examination, and for this purpose Rotch has suggested allowing the infant to lie on a pad of cotton with rubber underneath it, from which the urine may subsequently be squeezed.

The examination of the kidney itself should be most thorough, as in many cases swelling or sensitiveness to pressure is our only valuable diagnostic sign. By inspection we may occasionally, although very rarely, make out a lumbar swelling, as in certain cases of pyonephrosis and suppurative nephritis, especially if associated with perinephritis and paranephritis, while some claim that the absence of the kidney may be told by change in the contour of the flank. Percussion is rarely of help except in cases in which the enlargement is so marked that it can be made out better by other means; occasionally by inflating the colon through a rectal tube and percussion we may differentiate renal swellings from other tumors. Palpation is the most reliable method, and various procedures should be employed, the patient being made to exhale deeply, the legs somewhat flexed, and the patient sometimes lying on the back, sometimes on the side, occasionally standing; rectal and vaginal examination should be made at the same time, the latter

being especially important, since about one-half the ureter may be palpated by this method, and calculus, stricture, thickening, etc., determined. Sometimes, on account of pain, nervousness, very tight muscles, etc., the examination must be made under anæsthesia. The *x*-rays may be employed, although they are not of great value except in ureteral and renal calculi, especially those composed of phosphates or oxalates; by the use of a catheter coated with some substance impervious to the *x*-rays the course of the ureter may be determined, while in abscess of the kidney and marked sclerotic changes we may get a deeper shadow than normal, sometimes even simulating stone.

Some employ exploratory incision, puncture, or injection, the former being preferable, as puncture may be followed by hemorrhage or persistent fistula; by puncture, pus mixed with urine will determine the nature of the swelling, while after injecting methylene blue into the tumor, if the urine is colored green within a few minutes it shows that the kidney is the source of trouble.

The general symptoms in many cases first suggest the diagnosis. History of pain in the flank, often slight but usually elicited on careful questioning, has been present in most cases at some time during the course of the disease, often regarded by the patient as lumbago, or neuralgia; fever, malaise, sweats, chills, and digestive disturbances are important only in suggesting that some inflammation is present; if no other cause can be found, however, one should always think of pyelitis and renal suppuration, and the urine should be examined at once. In most of the inflammations of the kidney or its pelvis the leukocytes are increased; in mild cases of chronic pyelitis and pyelonephritis, open pyonephrosis, and encapsulated abscess leukocytosis may be absent.

In pyelitis, whether acute or chronic, the diagnosis can almost always be made with certainty by the use of the cystoscope and the ureteral catheter and by the examination of the urine, except in those rare cases of severe and rapid gangrenous or diphtheritic pyelitis consecutive to severe infection. It must not be forgotten, however, that pyuria may be due to causes outside the urinary tract, such as appendicular abscess, prostatic abscess, or pyosalpinx, rupturing into the bladder, ureter, or renal pelvis, and such uncommon causes must be eliminated, which is usually an easy matter.

In *acute pyelitis* the sudden appearance of localized pain associated with chill is an important sign, while in the chronic cases the previous history of the patient, especially constant pain in the flank or slight fever, is very helpful. The presence of polyuria usually associated with an acid urine of low specific gravity with pus cells in the specimen from the kidney will be sufficient to diagnose pyelitis. If the specimen is obtained from the bladder, especially if cystitis is present, we have no absolutely diagnostic sign of pyelitis; we found usually a relatively higher albumin content than could be accounted for by the pus and blood, although many investigators deny this disproportion. There is nothing characteristic in the epithelial cells.

The presence of casts and an increased amount of albumin points to pyelonephritis, although both of these, especially the former, may be wanting; as a rule, systemic disturbances become more marked with the involvement of the kidney. Casper rightly insists that the result of treatment is of great service in determining whether pyelitis complicates cystitis, and if no or slight improvement follows the appropriate treatment of the bladder this associa-

tion is suggested. The use of the cystoscope and the ureteral catheter can, of course, easily settle this point. Chronic pyelitis may occasionally very closely simulate renal tuberculosis, although careful bacterial studies should make the diagnosis definite.

Whether the condition is unilateral or bilateral can always be determined by ureteral catheterization, and usually by a careful history of the case. In pyelitis the functional ability of the kidney is not affected, as a rule, while in pyelonephritis it is usually lessened. Beer has suggested as a differential test the abnormal retention and delayed excretion of methylene blue in the latter affection. In the rare cases of croupous and diphtheritic pyelitis the diagnosis can usually be made from the characteristic findings in the urine, and the same is true if parasites, fragments of stone, or bits of new-growth are found in the urine. The differential diagnosis between kidney and bladder infections, on the one hand, and urethritis, on the other, is hardly worth considering, as the source of the pus can be easily differentiated by catheterizing the bladder and by milking the urethra.

In both pyelitis and pyelonephritis *lumbar pain* and *swelling* are most important diagnostic points; in the former disease the pulse is usually of normal tension and the heart of normal size, while in the latter high tension pulse, some tendency toward cardiac hypertrophy with arterial thickening, and retinal symptoms are often met with; the frequency of chronic interstitial nephritis in old people, however, makes the association in them of pure pyelitis and high tension pulse not at all uncommon. The possible complications of pyelitis and pyelonephritis are many, such as pyonephrosis, abscess of the kidney, perinephritis, paranephritis, contracted kidney, fistula of the renal pelvis, calculus, ureteritis, and peri-ureteritis. It is quite striking in how many cases, especially those in which acute exacerbations are marked, the diagnosis of appendicitis has been made, frequently followed by operation. Hunner has reported four cases in which the two conditions were associated, the appendicitis being primary, the pyelitis or ureteritis secondary and transitory.

In the miliary metastatic abscesses met with in the course of general infection a certain diagnosis is usually impossible; in a few cases pain or sensitiveness, pus cells and red blood cells in the urine, and oliguria or anuria, due to plugging of the tubules and glomeruli with bacteria, have called attention to the condition.

In all cases of *renal suppuration* the diagnostic difficulties are very great, yet in all the finding of the etiological factors, such as trauma, calculus, contiguous focus of inflammation, cystitis, urethral stricture, or prostatic hypertrophy, is helpful. The most important symptoms are the pain and swelling in the renal region and the pyuria. The presence of considerable albumin, pus cells and red blood cells, hyaline, granular, blood, pus, epithelium, and bacterial casts, and occasionally bits of necrotic renal tissue are our most valuable diagnostic signs if present, although their absence does not at all rule out renal suppuration. In *renal abscess* the sudden appearance of a large amount of pus in the urine, with a coincident decrease in the size of the tumor and usually in the constitutional symptoms as well, will give us the diagnosis. In encapsulated abscess, closed pyonephrosis, or complete destruction of the kidney by the disease the urine may be quite normal. It is not at all uncommon for the healthy kidney to be regarded as the diseased organ because of its compensatory hypertrophy.

In *purulent nephritis* and *pyelonephritis* the kidney as a rule is at first only slightly enlarged, although in the later stages it is usually sufficiently swollen to be made out by palpation; in empyema of the renal pelvis, and kidney abscess, the tumor is frequently large and fluctuating, and practically impossible to differentiate by palpation from hydronephrosis. In cases where renal suppuration is suspected von Bergmann suggests squeezing the kidney with the palpating hands, to see if by this means a large amount of pus is not expressed into the pelvis of the kidney and thence into the urine. In *pyonephrosis* persistent pyuria is the rule, or sometimes pyuria with periods of clear urine between, these latter being associated with increase of the swelling and of the constitutional symptoms. Cathelin reports a case of lumbar abscess from Pott's disease opening into the bladder exactly simulating pyonephrosis.

Prognosis.—The course and prognosis varies markedly in different cases, depending upon the character and virulence of the infection, the accessory etiological factors present, the drainage of the kidney, the presence or absence of complications, and the general physical condition. The prognosis, other things being equal, is better in pyelitis than in infections of the kidney substance, in cases in which drainage is good than in those in which urinary stasis is marked, in acid than in alkaline infections.

In *acute pyelitis* the course is usually rapid, the acute stage rarely lasting more than a few days; in very rare cases death may occur quickly, due to anuria with uræmia, although, as a rule, either cure takes place or the condition becomes chronic. If proper treatment is inaugurated cure is usual where the cause is transient or easily removed, as in the case of irritating drugs, while in the case of the acute infectious diseases, cystitis and inflammations of the kidney substance, the prognosis of the secondary pyelitis depends largely on the character and duration of the primary disease and the possibility of carrying out satisfactory therapeutic measures; in the acute pyelitis after cystitis, especially those cases due to the gonococcus or to the colon bacillus, or in those cases which follow urethral or ureteral catheterization, cystoscopy, or operations on the bladder, cure is not uncommon if treatment of the primary condition is prompt.

The course of *chronic pyelitis* is very variable; it may be present for many years, especially if the causal factors remain; the symptoms may be very slight, with no appreciable impairment of the general health, this being especially likely to occur in infections with the colon bacillus, and cases of chronic pyelitis of more than five years' duration without any appreciable loss of strength are not uncommon. On the other hand, the majority do not run so mild a course, while complete recovery is very unusual. This is especially so when the accessory etiological factors persist, as in hypertrophy of the prostate, vesical paralysis, etc. The course is subject to very marked variations as regards the symptoms, and marked constitutional disturbances are not infrequent; these exacerbations are sometimes due to definite causes, such as alcohol, intercurrent disease, or sudden chilling. If the infection is alkaline, symptoms of ammoniæmia may occur, although these are not common; in all cases the involvement of the kidney is liable to cause an increase in the severity of the symptoms and hasten the end.

In the writer's experience stone is always present in chronic infections due to bacteria which have the power to decompose urea; in 5 such cases, 3 due to *Bacillus proteus vulgaris*, 2 to the white staphylococcus, a phosphatic stone

was found in each, and in the 3 cases in which careful culture was made from the centre of the stone, a pure culture of the microörganism was found; in one case of infection with the colon bacillus a stone of uric acid and urates was found.

Simple pyelitis may go on for years without renal involvement, but if such involvement occurs the usual sequels of destructive renal changes occur; if the suppurative changes in the kidney are marked there is usually a marked increase in the severity of the symptoms, and of course much more so in the case of bilateral than unilateral infection; in some cases the pyelitis apparently clears, but an encapsulated renal abscess remains. If, on the other hand, the kidney is only slightly affected, the clinical picture in many cases is hardly appreciably changed.

In all cases the prognosis is worse with alkaline infections, because of the greater destruction of the mucous membrane, the possibility of ammoniæmia, and the probability of stone.

In the pyelitis of *pregnancy* spontaneous cure may occur, sometimes simply due to rest in bed, at other times after delivery, but in many cases a chronic pyelitis, sometimes associated with salpingitis, or a bacteriuria remains. In *children* spontaneous recovery is quite common.

In *suppurative nephritis* there are often no definite symptoms, while in other cases, if present, they are lost in those of the primary disease. The course is usually subacute or chronic except in those cases met with during the course of general infections. In this latter group of cases, as a rule, no special symptoms are seen, although oliguria or anuria may develop if the gomeruli and uriniferous tubules are packed with bacteria, thus adding the symptoms of uræmia to those of septicæmia; death occurs in practically all these cases due to the almost universally fatal termination of the general septicæmia, and to the fact that it is in the most severe types that the kidney is likely to be involved.

In *traumatic suppurative nephritis* the prognosis is fair if the pus can freely discharge into the renal pelvis, while if the discharge be external the symptoms may be mild, although here there is a great tendency to the formation of burrowing abscesses, retention of pus, etc., which finally end the patient's life. Practically the same course is followed in renal suppurations by extension, but the prognosis is much more serious.

Renal abscess, whatever be the cause, may last for a long period of time with practically no symptoms; sooner or later, however, in the majority of cases, rupture takes place into the renal pelvis with the development of pyelonephritis, pyonephrosis, or empyema, which may either run a chronic course or may end fairly acutely; perinephritis and paranephric abscess are frequent accompaniments of renal abscess, while myelitis and neuritis have been described secondary to it.

Cases of *pyonephrosis*, if unilateral, may last for years, although oftener the constitutional disturbances are marked and the course more rapid; the prognosis is much graver if both sides are affected, or if the second kidney undergoes degenerative changes due to the toxæmia. Cure may occur in pyonephrosis, and in large renal abscess by the complete destruction of the kidney and its conversion into a fatty, fibrous, or putty-like mass, but this is very exceptional.

In the renal suppurations the course may be, on the one hand, very mild, sometimes even with no definite symptoms, and, on the other hand, may be

associated with symptoms of the gravest kind; in all cases the prognosis depends largely upon the etiological factors, being better if they are transient or easily removed, as in the case of trauma or stone, than when the cause cannot be satisfactorily treated; the much more satisfactory treatment of prostatic hypertrophy and chronic cystitis within recent years has unquestionably improved the prognosis. We must not forget that the disease is very insidious, especially the ascending forms, and that while we are nursing ourselves in a false security because the symptoms are unchanged, marked disease in the kidney may be taking place, which will suddenly completely change the clinical aspect. Pure bacteriuria may cause renal inflammation if the local or general resistance is lowered, and these and other facts should accentuate the importance of an early diagnosis and prompt and satisfactory treatment. Küster mentions four favorable factors in the prognosis, the possibility of an early correction of the urinary stasis, youth, a strong constitution, and a unilateral lesion.

Treatment.—**Prophylaxis.**—To properly carry out prophylactic measures it is essential that we should recognize the usual etiological factors and remove them if possible; these may be roughly divided into two groups: first, those that lower the resistance of the kidney by producing retention of urine, trauma, congestion, etc., and second, those that furnish the infection either by direct extension, as in the case of contiguous foci of inflammation, or by metastasis, as in the case of distant areas of inflammation, or by an ascending urogenous infection. It is, therefore, important to avoid all irritating drugs; to use the greatest care and the most rigid technique in the use of instruments; to avoid introducing infection or producing trauma; to treat with care and promptness all cases of cystitis and gonorrhœa; to remove if possible all causes of urinary stasis, as by operation in urethral stricture, phimosis, and hypertrophied prostate, and hydraulic dilatation in the case of contracted bladder; to remove such causes of irritation as stone, foreign bodies, etc.; to use some form of urinary antiseptic, such as hexamethylene-tetramine after operations, especially if on the kidney, or if the patient has to be frequently catheterized, after severe labors, during typhoid fever, in bacteriuria, etc.; to give large quantities of water under these conditions, either by mouth or by rectum, as by the latter method most of the fluid is eliminated by the kidney within two or three hours. It is advisable to give plenty of water in severe febrile diseases, in pregnancy, and in the latter case to insist upon a certain amount of rest in the prone position, and, in addition, in this as in all other cases, to build up the patient's health, avoiding above all things constipation; in children and infants, especially girls, to give plenty of water, and to insist on great cleanliness of the genitals, always washing from the front backward. If ureteral catheterization has to be done for any purpose one should be most careful in the technique and make the patients drink considerable water beforehand. Floating kidneys should be treated; in cases of vesical paralysis catheterization should be avoided as long as possible. In regard to the hæmatogenous renal suppurations prophylactic measures, as a rule, cannot be carried out successfully except in those cases in which the kidney is secondarily involved from some localized focus of inflammation; in such cases thorough and prompt opening and drainage will unquestionably lessen the probabilities of metastatic involvement of other organs. In the traumatic cases prophylaxis is most important, asepsis and antisepsis in regard to the treatment of the local

wound, rest, appropriate diet, plenty of fluid, and some of the urinary antiseptics. Many of the cases of infection by contiguity could unquestionably be prevented by prompt and thorough treatment of the primary focus of inflammation.

In the treatment of inflammations of the kidney and its pelvis it is essential that the causal factor should be recognized and removed if possible. In all cases the resisting power of the patient is to be increased by careful attention to the general health, correcting any disorders that may be present, especially digestive disturbances, constipation and anæmia.

In acute pyelitis and pyelonephritis the removal of the cause is sometimes sufficient to produce a rapid cure. The patient should be kept in bed at an equable temperature, it being especially important to avoid chilling; the diet should be simple, a milk or buttermilk diet being often best; all irritating drugs, highly seasoned food, and beverages containing alcohol should be avoided; an ice-bag may be applied, although a hot-water bag or hot moist applications are, as a rule, more grateful to the patient; warm baths or sweats sometimes give much relief; while if the fever is high, phenacetin, quinine, or some other such remedy is indicated, these being more effective than cold sponges. If the pain is very severe, dry or wet cups or very hot compresses may be tried, although usually recourse will have to be had to morphine or opium, either by mouth, hypodermically, or by suppository. The bowels should be kept freely open and the patient made to take much water, while if the stomach is upset, salt solution may be given by enema or, in very severe cases, by infusion. The water dilutes the urine, washes out the mucus and often helps to dissolve it and carry away the bacteria and toxins. In place of the water some use cream of tartar solutions, linseed tea, etc.

The urinary antiseptics are practically always indicated—hexamethylenetetramine (urotropin), salol, etc., in doses of from 5 to 10 grains three or four times daily, with the usual reduction in doses in the case of infants and children; these drugs are peculiarly valuable in acute infections. Sleeplessness and nervousness may be helped by the bromides, trional, or veronal. If the urine is acid, bicarbonate or citrate of soda or potash may be given; if alkaline, boric, benzoic, or camphoric acid, as it is probable that the growth of the bacteria is inhibited in a medium of different reaction from what it is accustomed to.

If the cause has been removed, many cases of acute pyelitis and pyelonephritis will be cured under the above treatment; if the severe symptoms persist, however, nephrotomy may be necessary, especially in ascending infections, or metastatic lesions where the primary focus is no longer active.

In chronic pyelitis and pyelonephritis, if the cause has been determined, it must be treated promptly. The resisting powers of the patient are to be increased by the usual procedures, correcting disorders of digestion or nutrition, constipation, anæmia, etc. The medicinal treatment consists in the administration of urinary antiseptics, or of the astringents, lime water, lead acetate, gallic or tannic acid, etc., or of such drugs as uva ursi, the balsams of copaiba and Peru, etc. Of these drugs, urotropin or hexamethylenetetramine or its derivatives may be taken for a long period of time without doing apparent harm, although some claim that it should not be used in gouty or lithæmic subjects, or where uratic calculus is present, and Karwowski has collected 13 cases of hæmaturia and 2 of pyuria after urotropin. Almost all the other drugs, however, can be used but a short period of time,

as they are likely to produce marked digestive disturbances. In all cases of chronic pyelitis or pyelonephritis some of the urinary antiseptics should be unquestionably tried, as they usually prove very useful, but the drugs of the other groups are but little used, as they do little if any good in the majority of cases, besides deranging digestion; in persistent, intractable cases, where the other means have been unsuccessful, they may be tried, however, Senator in this connection advising a lead and opium pill, one or two grains of each, three times daily. Obviously in the case of the antiseptics the effect on the deeper tissues is much less than on the pelvic mucous membrane, and they are, therefore, of less value when the kidney itself becomes involved in the infectious process. It is wise to change the reaction of the urine by giving alkalies or acids by the mouth, while here, as in acute pyelitis, large amounts of pure water, or of the alkaline, alkaline-saline, or lithia waters, should be administered; if the kidney itself is much involved, however, one should avoid giving too large amounts. In cases of ammoniacal decomposition chlorate of potash, boric, benzoic, or camphoric acids may be given.

The diet should be bland and light, although, of course, meats and other solid foods are to be taken, and alcohol, strong condiments, and irritating foods should be avoided. The pain, as a rule, is not great except in acute exacerbations, and is usually relieved by hot compresses, a hot-water bag, or the Paquelin cautery; occasionally phenacetin, codeine, or even morphine must be used.

In the pyelitis and pyelonephritis of pregnancy artificial labor must be induced, or a nephrotomy or even nephrectomy performed if the symptoms are very severe and very persistent and do not yield to the usual treatment. Dilatation of the bladder sometimes gives marked relief in this as in other forms of renal infection. Sometimes the patients are much benefited by a cure at one of the alkaline springs.

The acute exacerbations are to be treated in the same way as acute pyelitis, but unfortunately cure is extremely rare in the chronic forms of the disease, although by the above method of treatment the symptoms are usually markedly improved and sometimes entirely disappear; nevertheless examination will usually show that infection is still present.

Recently chronic pyelitis has been treated by Kelly, Casper, and others by instillation into or irrigation of the renal pelvis through the ureteral catheter, the results in most cases being most encouraging, especially in infections with the colon bacillus or the gonococcus. Solutions of boric acid or of nitrate of silver (1 to 2000 to 1 to 1000) may be used every few days as an irrigation, or 5 cc. of a 1 to 2 per cent. solution of silver nitrate instilled; by these means a number of cures have been reported, Casper obtaining a cure in 12 stubborn cases, 9 due to the gonococcus, 3 to the colon bacillus. If we have pyelonephritis or if the pyelitis is associated with tuberculosis or calculus, this treatment can only be palliative and should not be employed.

The recent work on the *vaccine* treatment of disease should suggest similar treatment in infections of the kidney, especially since a permanent cure is difficult or impossible to attain in the vast majority of the chronic cases by the means which have been hitherto employed. The vaccine should be made from the microörganism isolated from the patient's urine; the writer has employed this method in three cases, one due to the colon bacillus and two to *Bacillus proteus vulgaris;* but the results, while encouraging, were

not conclusive, due to the short period of time in which the treatment was employed. In all three cases the clinical symptoms and the urinary findings were undoubtedly improved while the treatment was being administered; the dosage employed was from 150,000,000 to 500,000,000 of the dead bacteria given hypodermically once or twice weekly. This method should be employed farther in the hope that some of the otherwise incurable cases might be relieved, while the serum treatment should also be tried, especially in typhoid and streptococcus infections.

In certain cases *operative* treatment may be necessary, either nephrotomy, nephrectomy, pyelotomy, or resection. If the kidney is only moderately affected, a nephrotomy, pyelotomy, or resection should be attempted; if almost entirely destroyed, a nephrectomy. In all cases, however, it is essential that the presence and the functional ability of the other kidney be determined before the operation is performed. In double pyelonephritis, if the conditon warrants it, operation may be performed first on one kidney, and at a later time on the other, the kidney being opened, washed out, and drained. If the pyelonephritis is associated with abscess formation, free opening and drainage or nephrectomy is indicated according to the extent of the process. Some brilliant cures in the case of unilateral pyelitis and pyelonephritis have been reported after nephrotomy.

In suppurative traumatic nephritis, and by extension from neighboring infections or by metastasis from a distant focus of inflammation, the two main indications are to remove the cause if possible or to lessen its manifestations, and to make an early and free outlet for the pus. Although spontaneous cure is possible, nevertheless this occurs in such a small proportion of these cases that unless the pus has already found a free and satisfactory outlet, operative treatment is imperative; in the renal suppurations secondary to general infections, pyæmia, septicæmia, ulcerative endocarditis, etc., treatment of the kidney itself is obviously contra-indicated, as in the rare cases in which the primary disease is cured, the kidney, as a rule heals spontaneously.

The removal of the cause of inflammation is in most instances more important prophylactically than therapeutically; the early and proper treatment of some nearby or distant focus of inflammation, the irrigation of the bladder in cystitis, regular catheterization with the greatest care or emptying the bladder by manual pressure in vesical paralysis, operative treatment in enlarged and urethral stricture, the removal of vesical neoplasms—all these procedures may, in the first place, prevent renal infection from arising, while if it has already developed, lessen markedly the severity of its manifestations, and hasten the cure if that is possible. If an abscess arises after trauma the wound should be widened, washed out, and drained, while in only very severe cases is resection, nephrectomy, or nephrotomy necessary. In cases of pyelonephritis, whether due to ascending or descending infection, we should first try the measures already described, diet, rest, the use of alkaline waters, urinary antiseptics, etc.; in many cases great relief is obtained by these methods, but if marked suppuration occurs operative treatment is necessary. In suppurative nephritis and pyelonephritis with the formation of abscesses, operative treatment should be employed as early as possible, but not until the presence and the functional ability of the other kidney has been determined, even if an exploratory nephrotomy is necessary, although usually the results obtained by ureteral catheterization are sufficient.

The possible operations are pyelotomy, pyelostomy, nephrotomy, nephrostomy, resection of the kidney, and nephrectomy. If the ureter is narrowed or closed, nephrostomy or pyelostomy should be done and an attempt made to dilate the constricted portions of the ureter from above; persistent fistula is a frequent sequel to these operations. On account of the well-known regenerative powers of the kidney, resection or nephrotomy should be the operation of choice if only a comparatively small and localized portion of the kidney is markedly affected by the disease. When nephrectomy is done, as much as possible of the diseased ureter should be removed at the same time, although this is not so important as in the case of tuberculous infections. It is always justifiable to perform these smaller operations first, and later a secondary nephrectomy if necessary; a primary nephrectomy should practically never be done if the second kidney is diseased, for a nephrotomy with drainage of the more diseased organ will often give an opportunity for the patient's general health to be improved, so that the secondary nephrectomy, if found to be necessary, will offer a better prognosis. In pyonephrosis, nephrotomy or nephrectomy is usually necessary, although irrigation of the renal pelvis may be very beneficial in a small proportion of the cases; this latter procedure is obviously of little use where the renal substance is involved and the abscess cavities do not connect freely with the renal pelvis.

Rovsing concludes that death from insufficiency of the other kidney should never occur if the modern methods of diagnosis are carefully and intelligently employed; if the urine is free from pus, albumin, and bacteria, the kidney may be regarded as normal, while the presence of pus and bacteria usually contra-indicates operation on the other kidney; albumin without pus and blood, according to Rovsing, is often simply a sign of toxæmia, and is a strong indication for operation. The functional tests, although not so important as the microscopic, chemical, and bacteriological findings, should be employed wherever possible in all cases where operation is under discussion, for if the findings by this method are positive they are of unquestionable value.

As to the results of the operative treatment of suppurative nephritis and pyelonephritis, Küster gives the following figures: In 100 nephrotomies, 27 were cured, 56 were unhealed, and in 23 of these a secondary nephrectomy was done, 17 died; 2 cases of resection each gave favorable results; in 143 lumbar nephrectomies there were 24 deaths, and in 7 transperitoneal nephrectomies, 4 deaths.

PERINEPHRITIS—PARANEPHRITIS—EPINEPHRITIS—PARANEPHRIC ABSCESS—PERINEPHRIC ABSCESS.

The words perinephritis, paranephritis, and epinephritis have been used loosely to signify indiscriminately inflammation of the perirenal tissues, while Rayer, who first differentiated inflammation of the perirenal tissue from that of the kidney, first made use of the term perinephric abscess. It is better to be more explicit, however, and to define perinephritis as inflammation of the fibrous capsule immediately surrounding the kidney; epinephritis, inflammation of the fatty capsule, and paranephritis, of the retroperitoneal fat. Of the three forms of epinephritis described by Israel (exclusive of the tuberculous, the syphilitic and actinomycotic), which he calls fibrosclerotic, lipo-

matous, and phlegmonous, the first two are so extremely rare, and the last, the very important phlegmonous form, so frequently, in fact nearly always, gives rise to paranephritis that it is wise to consider epinephritis and paranephritis together under the one term paranephritis, as used by many of the older clinicians.

Perinephritis, although very rarely an independent disease, and in the vast majority of instances secondary to various inflammations of the kidney or of the perirenal fat, is of great interest because, due to the dense adhesions formed and the inability of the capsule to be easily moved over the kidney surface, symptoms almost exactly like those of renal colic may be produced, especially if the organ becomes congested; this is the probable explanation of many obscure cases of colic, in which operation does not reveal stone, new-growth, or abscess.

Paranephritis, and we are now using the term to include inflammation both of the fatty capsule and of the retroperitoneal fat behind the kidneys, while the much less common condition, is of far greater importance, as it gives rise to paranephric or perinephric abscess. Perinephritis and paranephritis often occur together, although the process almost always begins either in the fibrous capsule, the fatty capsule, or the retrorenal fat, extending then to the others.

As to the frequency of the condition Küster has collected 230 cases of paranephritis, finding that it is twice as frequent in men as in women, equally frequent on either side, and that most cases occur between the ages of twenty and forty years; only 4 or 5 cases have been reported in which both sides were affected. Nieven, in a series of 138 cases, found 97 in men, 47 in women, and in a series of 166 cases, 26 in children up to thirteen years, the youngest being five weeks old; 5 cases were found between the ages of sixty and seventy years, while the greatest number were met with in the fourth decade; in 136 cases the right side was affected 76 times and the left side 60 times.

Etiology.—Paranephritis may be either primary or secondary, the former usually developing from penetrating wounds and injuries of the kidney and perirenal tissues, the latter usually arising from metastasis or extension of inflammation from neighboring organs or tissues. Among the causes of the so-called primary form may be mentioned: penetrating wounds and various contusions, blows in the region of the kidney, lifting heavy weights, sudden strain, hard riding, in fact, any conditions which may cause a slight tear with associated hemorrhage into the perirenal tissues, this acting as a nidus for infection if any bacteria are brought there by the blood stream; foreign bodies from the intestine have been the cause in a few cases, while in some cases exposure to cold is the only causal factor that can be made out.

The so-called secondary form arises either by metastasis, the infection being carried by blood or lymph current or by direct extension from some neighboring focus of inflammation or suppuration. Thus, it has been met with during or after many infectious diseases, puerperal fever being one of the most important in this connection. Küster believes that the cases met with in contagious diseases are not due to the primary disease, but to a secondary infection with pyogenic bacteria. In all these cases it is not known whether the kidney or its capsule is affected first.

The most common cause of paranephritis by direct extension is purulent inflammation of the kidney itself, while among other causes may be men-

tioned various suppurations in the pelvic cavity, such as parametritis and rectal abscess, appendicular abscess, psoas abscess, etc. Operations on the bladder and the genitals are followed occasionally by paranephritis. Of course, bacteria are always the immediate cause of the inflammation, and among those found in paranephric abscess may be mentioned staphylococci, streptococci, the pneumococcus, and colon, typhoid, tubercle, and influenza bacilli.

Pathology.—We are rarely able to study the early stages of paranephritis, but probably there is no difference between this and inflammations elsewhere except that in the traumatic cases the inflammation is probably preceded by small hemorrhages into the fat, this in turn being followed by the usual phenomena of inflammation. When seen at operation or autopsy we usually find the fatty capsule and retroperitoneal fat converted either into one large abscess, or into several smaller abscesses separated from each other by more or less necrotic fat and connective tissue. Maass insists that in the early stage indurative changes are very likely to occur, making it sometimes difficult to differentiate this stage from tuberculosis of the perirenal tissues; this would account for the tendency which the pus shows toward burrowing, opening either outward or into various organs. The pathological picture is similar to that met with in other abscesses, and a distinct pyogenic membrane is often seen if the condition has been present for a considerable length of time. The retroperitoneal fatty tissue is especially likely to be the seat of the pus, the upper and lower poles are frequently affected, while that portion anterior to the kidney is rarely involved, although if it should be we will often find a circumscribed local peritonitis, and occasionally a general peritonitis due to perforation. An abscess in the true fatty capsule tends to burrow along the ureter toward the pelvis, while one of the retrorenal fat points more toward the inferior or superior lumbar triangle. The pus is sometimes odorless, sometimes has a fæcal odor, due probably to proximity to the large intestine, or it is putrid if gangrene has occurred. The abscess cavity contains pus and blood, often necrotic, small masses of fat, sometimes fatty crystals, degenerative connective tissue, and shreds or masses of necrotic tissue. The kidney is usually pushed forward and upward, and it may become congested or with its capsule may undergo various inflammatory changes, although, as a rule, the fibrous capsule protects it for a long time. We may find amyloid degeneration of various organs, or pleurisy with effusion on the affected side if the condition has lasted long.

Symptoms.—In the majority of cases, due to the fact that the lesion is so deep seated and that the symptoms are usually masked in the early stage at least by the primary disease, an early diagnosis is difficult to make. In certain cases of insidious infection of different parts of the body, however, the first symptoms may be referred to the paranephric region, and only later the fact made out that the primary focus of infection is elsewhere. If the condition follows injury, the symptoms are more likely to be referred definitely to the paranephric region, pain usually being the first symptom. In the secondary cases as the disease progresses the true nature of the lesion usually can be made out. The three important symptoms are pain, lumbar swelling, and fever. The *pain* is usually the first symptom, often extremely severe, localized in the lumbar region, and increased by every movement, and by direct pressure. The *fever* may be remittent or intermittent, the usual condition, or it may be continuous, high or low, or absent altogether.

The *local swelling* usually first appears in the back, and by palpation a smooth, elastic, usually fluctuating mass, generally fixed, and not affected by the respiratory movements, can be made out. It is, as a rule, more diffuse, not so well defined, and not so distinctly limited as a renal tumor. The skin is often œdematous if it points outward, while it may also become distinctly reddened and swollen when the inflammation gets near the surface.

The urine, as a rule, is normal except in those cases where the primary disease is one of the kidney or its pelvis. The general symptoms are those usually found in abscesses, that is, chills, frequently repeated in many cases, loss of appetite, loss of weight, vomiting and various digestive disturbances; sometimes, due to pressure on the colon, constipation is present, while we may have flexion of the hip due to irritation of the psoas muscle. The swelling may extend upward toward the diaphragm, or downward toward the pelvis and iliac fossa, while if rupture does occur we may have diarrhœa and tenesmus, painful, frequent urination, or dyspnœa according to the seat of the rupture, although rupture may occur with no symptoms whatsoever. After rupture the size of the tumor may diminish and the pain disappear. As to the localization of the seat of the abscess, Maass, Roberts, and others have mentioned special symptoms; thus, difficult breathing with persistent vomiting and pleuritic pain would suggest suprarenal abscess; constipation and flexion of the hip, infrarenal; pain on pressure and early lumbar tumor, retrorenal; while there are no typical symptoms, except possibly those of a local peritonitis, to suggest an abscess in front of the kidney.

Course.—The primary and secondary forms of the disease differ markedly as to course and duration, the former usually beginning suddenly with a fairly rapid course, the latter being slow and insidious. In every case the course is dependent upon the position of the abscess, the direction of its burrowing, the character of the primary disease, and the associated complications; early external rupture in the lumbar region, and early operative treatment are important factors in shortening its duration. The pus may burrow along the psoas muscle to Poupart's ligament, along the ureter into the bladder, or may rupture into the intestine, especially the cæcum or colon, ureter, peritoneal and pleural cavities, and in many cases fistulæ occur, which, although persisting a long time, usually spontaneously heal. In rare instances the kidney may undergo gangrene due to thrombosis of its vessels, or an atrophic nephritis may be caused by the contraction of the inflamed perinephric tissue. Rosenberger has collected 26 cases of perforation: 6 into the intestine, with 2 deaths; 13 into the pleural cavity and lungs, with 8 deaths, and 3 into the peritoneal cavity, with 3 deaths. Even in favorable cases the duration of the disease is several weeks, while in the unfavorable ones, especially those secondary to causes which persist, the condition may last for years, and death may finally supervene, either by pyæmia or septicæmia, by gradually wearing out the patient, or by the development of amyloid degeneration of the various viscera.

Diagnosis.—Early diagnosis is always difficult because, in the first place, the most important symptom, tumor, cannot be made out early, and in the second place, the symptoms are usually masked by those of the primary disease; especially difficult are the rare cases without fever. Pain, the first symptom, is frequently regarded as due to lumbago, although in the latter disease this is usually bilateral, less likely to be associated with leukocytosis, and is usually not so definitely localized in the soft parts. The general

symptoms often suggest one of the acute infectious diseases. It is always well to remember, as Israel insists, the fourfold character of the symptoms in paranephritis, the general toxæmia, localized symptoms, such as pain, those due to the extension of the abscess, and those due to acute metastatic involvement of the kidney, such as vomiting and changes in the urine. Even with pain, fever, and localized swelling the condition must be differentiated from all other causes of similar signs and symptoms in this region; this is especially so in the case of inflammations of the kidney itself, but here the examination of the urine, and the fact that in paranephritis the swelling is less distinctly limited, is usually retrorenal, and is affected little by the respiratory movements, should be helpful in making the diagnosis. Differentiation of paranephric abscess from diseases or displacements of the liver, spleen, ovary, or intestine can usually be accomplished; the leukocytosis is often helpful here. When the swelling comes near the surface the overlying skin is usually œdematous, while flexion of the hip is frequently found; the urine is normal, unless the disease is consecutive to a pyelitis or pyelonephritis. In distinguishing other abscesses in this region, extensive appendicular, psoas, and parametritic abscesses and abscess of the subcutaneous tissue, great difficulties may be experienced, although usually a careful examination with a consideration of the etiology and course of the disease will make the diagnosis certain. In doubtful cases puncture is justifiable, and if there is much admixture of fat with the pus we are probably dealing with a paranephric abscess. In a few cases the use of the *x*-rays may be helpful.

Prognosis.—This depends on the conditions surrounding the especial case, being most favorable in those cases pointing outward, or where surgical interference is early, and thus, as a rule, good in the primary type of the disease, and least so when the pus is difficult to recognize or to reach, when the primary disease is intractable, or when complications occur. The prognosis is peculiarly dependent upon the skill of the physician in making an early diagnosis. In Küster's series of 230 cases of paranephritis there was a complete cure in 145, a persistent fistula in 6, while death occurred in 79, that is, 34 per cent. of the cases.

Treatment.—Before the diagnosis can be made with certainty some of the symptoms, notably pain and fever, require treatment. We may use the Paquelin cautery, hot and cold applications, cupping, various drugs, aspirin, phenacetin, the salicylates, etc.; with very intense pain morphine must be given hypodermically. It is highly improbable that any of these measures have the least effect on influencing the disease. As soon as the diagnosis can be made with certainty there is but one course to pursue; the abscess must be freely opened and drained, its cavity explored so that all pockets of pus can be broken down, while if there is any question of the kidney being also involved it must be investigated by palpation, or by incision, and nephrotomy or nephrectomy be done if necessary.

URETERITIS—PERI-URETERITIS.

With few exceptions inflammation of the ureter occurs only in association with an ascending infection from the bladder or a descending infection from the kidney and its pelvis, and for that reason as independent affections ureteritis and peri-ureteritis are of small moment, their symptoms being

practically included in those of the primary disease. Pyogenic inflammations of the kidney and its pelvis, except those of a transitory nature, practically always involve the ureter to a certain extent, although often only the upper portion is affected, while ureteritis consecutive to bladder inflammations is less common. As to its etiology, the causative factors are the same bacteria which give rise to pyelitis on the one hand and cystitis on the other. Israel, White, Stein, and Viertel have each reported cases of primary ureteritis, the symptoms being those of a nephralgia with hæmaturia, while a chronic proliferating ureteritis of doubtful etiology has been described. Tuberculous ureteritis is especially important, for in most cases of renal tuberculosis the ureter becomes involved, often along its whole course, so that the nature of the disease may be revealed by a cystoscopic examination; whether tuberculosis of the bladder can infect the ureter and subsequently the renal pelvis by direct extension is still a matter of discussion, although certain findings are difficult to explain otherwise. Among other etiological factors of importance may be mentioned various new-growths and areas of inflammation in the neighboring tissues, pyosalpinx, appendicular abscess, etc., and especially ureteral calculus, for whether primary or secondary, the ureteral wall may be so injured that inflammatory changes will be easily set up if pyogenic bacteria are present. Those cases of ureteritis and peri-ureteritis due to extension of inflammation from some nearby focus are interesting, as when such infection occurs from the inflamed appendix, and such cases are especially important because of the possibility of overlooking the primary disease.

The ureter is usually markedly thickened, especially in tuberculous ureteritis, and if the lower portion is affected the vesical orifice is swollen, œdematous, or ulcerated. Frequently the peri-ureteral tissues are involved, and we have a peri-ureteritis, or rarely a peri-ureteral abscess, which may require opening and drainage. The mucous membrane of the ureter may be œdematous, infiltrated, or ulcerated, while it is very common to meet constriction of the lumen, sometimes complete closure, kinking of the ureter in its course, or dilatation, the latter being especially likely to occur above a stricture or an impacted stone, and sometimes leading to hydronephrosis, pyonephrosis, or pyo-ureter.

Symptoms.—The symptoms of ureteritis and peri-ureteritis ordinarily met with in association with kidney or bladder infections are of no especial significance, but it must not be forgotten that stricture of the ureter may produce symptoms simulating very closely those of nephrolithiasis or nephralgia. The *course* of ureteritis is practically the same as that of the primary disease, and yet it undoubtedly plays an important role in the development of complications; thus, stricture of the ureter will lead to dilatation of the renal pelvis, and hydronephrosis or pyonephrosis if the occlusion is marked, while if associated with stone, or even without such association, a complete closure may occur, leading to a stoppage of the urinary flow from the affected kidney and sometimes a complete anuria due to reflex inhibition of the other kidney. In diseased conditions a reflux of fluid from the bladder can undoubtedly occur, and thus the ureter plays a very important intermediary role in the development of pyelitis and pyelonephritis consecutive to cystitis.

Diagnosis.—The diagnosis may be safely made if the physical signs, especially the urinary findings, show the presence of pyelitis or pyelonephritis, while in cases of cystitis which do not yield satisfactorily to treatment, a

ureteritis and probably also a pyelitis may be suspected. In such cases a cystoscopic examination of the ureteral orifices with the use of the ureteral catheter is of paramount importance, while in the case of women the thickened ureter met with in ureteritis, especially in the tuberculous form, may be palpated through the vagina. Ureteral strictures and kinks may be made out easily by ureteral catheterization, Kelly even measuring the tightness of the stricture by a carefui estimation of the pull on the catheter or the resistance to its withdrawal, while if the *x*-rays are used in conjunction with a catheter impervious to these rays the course of the ureter may be accurately determined. In cases where stone is suspected as a causative factor, by means of the wax-tipped catheter or the *x*-rays its position may be determined, especially if the stone is composed of phosphates, oxalates, or carbonates. In the case of the *x*-rays we must be careful not to mistake a phlebolith for such a stone. It is possible if there is infection only of the lower portion of the ureter to find pus in the urine if the ureteral catheter is inserted but a short distance, while if it is pushed beyond the infected area the urine is clear.

Treatment.—The treatment is closely connected with that of the primary disease. It is well to remember the frequency with which the ureter is involved in infections of the kidney and its pelvis, for many failures have resulted from a lack of appreciation of this fact, especially in cases of tuberculous infection. It is therefore essential, if nephrectomy is done, that if possible the diseased portion of the ureter be removed at the same time, even if this requires a complete ureterectomy with removal of a portion of the bladder wall; this is peculiarly so in cases of tuberculous nephritis and pyelitis. Peri-ureteral abscess must be treated by incision and drainage, either externally or in the case of women by the vagina. If stone is associated with ureteritis, ureterotomy, ureteronephrotomy, or ureteronephrectomy must be done according to the size and position of the stone and the condition of the kidney. In such cases, as well as in stricture of the ureter due to other causes, resection and anastomosis have been done, although in most cases a fistula remains. Occasionally operative treatment can be better carried out through the bladder, the perineum, or the vagina.

CHAPTER XII.

TUBERCULOSIS OF THE KIDNEY.

By THOMAS R. BROWN, M.D.

Tuberculosis of the kidney is met with in two distinct clinical forms: First, as part of a general miliary tuberculosis, both kidneys as a rule being involved, and the renal disease being usually of comparatively slight significance, because it is but a part of the general infection and its symptoms are usually lost in those of other organs; and second, the so-called primary renal tuberculosis, in which the disease is confined mainly to the urinary apparatus. Obviously the term primary is used in a clinical rather than in an etiological sense, as it is questionable if there are any cases of primary renal tuberculosis in the true sense of the word, and Krönlein, therefore, suggests the terms combined and solitary to describe the two forms. This clinical differentiation, however, is of the utmost importance, as our attitude toward the two is absolutely different. In one there is practically nothing to be done, and the diagnosis, made with great difficulty, if at all, helps little, if any, in our subsequent treatment, while in the other form the health and life of the patient depend upon a proper appreciation of the condition and an early diagnosis, for in this form prompt and proper treatment is followed by brilliant results in a large proportion of cases. It is, therefore, this second form of the disease, primary, primitive, or solitary tuberculosis of the kidney, or chronic localized tuberculosis, to which most attention should be directed.

The conception of this disease has absolutely changed; indeed, it is because of the early misconceptions of the etiological factors that progress in its rational treatment dates back only two decades or less. For many years the character of the disease was entirely misunderstood, and the reasons for this were manifold; in the first place, the disease as seen by the pathologists was usually advanced, bilateral and incurable, and generally associated with considerable involvement of other organs; in the second place, for a long time tuberculosis was supposed to be peculiarly liable to affect the genito-urinary tract in its entirety, and hence the popular but misleading phrase urogenital tuberculosis; while in the third place it was thought that in the great majority of cases the kidney was infected from the bladder secondarily by an ascending or urogenous route—all these views obviously suggesting the inadvisability of local treatment. These views were entirely incorrect, for the so-called primary form of the disease is in its incipiency almost always unilateral; it is only infrequently associated with genital tuberculosis, and even then there is rarely any direct connection between the two; it is usually due to a hæmatogenous or descending infection, the kidney being affected first; in its early stages at least the primary source of infection, a tuberculous gland, etc., is often of slight moment, and the prime requisite for successful treatment is its early recognition—in this respect differing in no wise from tuberculous lesions elsewhere.

Treatment must, of necessity, be mainly surgical, and yet the success of the surgeon is absolutely dependent upon the acuteness and skill of the physician in making an early diagnosis and in appreciating the underlying pathological process. Exactly why the tuberculous process should engraft itself upon one system, and remain confined to that system for a considerable period of time, we do not know, but the urinary system is no exception to this rule, and it is surprising for how long a time tuberculosis of the kidney alone, or of the kidney, ureter, and bladder, may persist without any active manifestations of the disease elsewhere. It is because of the ever-widening appreciation of these facts that the prognosis in renal tuberculosis is becoming progressively better.

Historical.—Struma and scrofula of the kidney were described by many of the older writers, Morgagni having given quite full descriptions of the disease, although Bayle went into greater detail and noted the identity of the picture in the kidneys and in tuberculous conditions elsewhere, incidentally a view only universally accepted within comparatively recent times. Howship's careful description of the disease and his differentiation of it from other renal inflammations marked a distinct step forward, shared in by von Ammon and Rayer; it was not, however, until the discovery of the tubercle bacillus that a real appreciation of the pathology of the condition could be had and the diagnosis made with absolute precision. In 1871 Simon gave a great impetus to renal surgery by performing the first extirpation of the kidney, while thirteen years later Morris recommended this operation in unilateral renal tuberculosis. The brilliant monographs of Israel, Krönlein, Kümmell, and Rumpel have placed renal tuberculosis upon a firm foundation as regards both diagnosis and treatment, although there is still a singular lack of appreciation by the medical fraternity at large of its frequency and the brilliant results which may follow its early recognition. Kelly gives the following dates as important in the development of our knowledge of renal tuberculosis: The stimulus to surgical thought given by Simon's first renal extirpation, in 1871; the discovery of the exact methods of diagnosis, from 1876 to 1893; the period of the development of the surgical technique in the hands of a few specialists, from 1890 to 1900; while from the last date the perfected operation has been in the hands of surgeons at large, and it may be added the methods of making a proper diagnosis in the hands of the entire profession.

Etiology.—The only question under discussion is that relating to the origin of the primary form, for in the case of acute miliary tuberculosis and the involvement of the kidney in the terminal stages of tuberculosis elsewhere the mode of infection is, of course, hæmatogenous, the renal disease being but part of a general tuberculosis. The etiology of the disease in that type in which the involvement of the urinary system dominates the picture is of the utmost importance, and on it depends the rational treatment to be employed. There are three possible ways in which the kidney may become infected by tubercle bacilli: (1) The hæmatogenous or descending route; (2) the ascending or urogenous; and (3) infection by continuity from some adjoining focus. The last of these, though interesting, is extremely rare and of slight clinical importance; cases have been described of extension of the disease from spinal caries, tuberculous empyema, tuberculosis of the adrenals, of the intestines, and of the peritoneum. In this connection the suggestion that renal involvement following vesical tuberculosis may be by continuity through the course of the ureter is of interest.

The relative importance of the ascending and descending modes of infection in renal tuberculosis has been the subject of much discussion. Guyon and many of the older clinicians taught that hæmatogenous infection was extremely rare, that, as a rule, the kidney was infected from the bladder by an ascending infection through the medium of the urine, that renal tuberculosis was, in the male at least, but a part of a general urogenital tuberculosis, that both kidneys were affected, as a rule, and that treatment was of little or no avail. The work of Baumgarten, Albarran, Israel, and others has shown how erroneous these older views were, and has given us the proper conception of the pathogenesis of primary renal tuberculosis. This question cannot be answered by studies made at autopsy, nor by the observation of the symptoms; in the former the disease has usually left its early stage far behind, and, as a rule, involvement of many other organs has taken place, in the latter the symptoms are apt to be most misleading, as the disease may remain dormant and practically without clinical manifestations until the ureter and bladder become involved. To answer this question, therefore, we must have recourse, in the first place, to the most careful clinical observations and the use of the modern instruments of precision; in the second place, to a most minute examination of the diseased organ if it should be removed at operation; and in the third place, to careful animal experiments.

Baumgarten by animal experiments showed that the infection is tuberculosis, travels with the current, not against it, in other words, from the kidney to the bladder; that in the genital tract the epididymis is the favorite seat of primary infection, but that the involvement of the two systems is quite independent of each other, although the bladder may be infected in either case, very rarely, however, from the genital system. Walker has inoculated the bladder of several hundred rabbits with bovine tubercle bacilli, and although his experiments have not yet been completed, they show that the kidney is practically never affected by an ascending pyelitis or pyelonephritis; he found in his entire series only one case which could be ascribed to this mode of infection, and showed that the ureter is often affected, although generally showing but simple dilatation, and that the urinary organs were affected very rarely from the genitalia. Israel reported four cases of tuberculosis of the epididymis and the kidney on the same side without involvement of the bladder, showing that tuberculosis of the kidney and genital apparatus may occur together without extension from one to the other, both in all probability being independent infections of hæmatogenous origin, although it is not at all impossible that hæmatogenous infection from one to the other may occur. To quote from the same author: "A large number of cases of tuberculosis of the urinary apparatus show that the kidney is either the only or the first affected portion," and he bases these conclusions on the following facts: postmortem tuberculosis of the kidney with no other disease of the genitourinary apparatus; lasting health of the patient after removal of the tuberculous kidney; the localization of the tuberculous changes in the bladder about the ureteral orifices; and the presence of fresh early tuberculosis limited to these same localities.

Many cases have been regarded as ascending infections because of the greater development of the process in the papillæ, the pelvis, or the ureter, but this argument is fallacious, because the changes in the medulla are often secondary to some primary focus in the cortex, although the medullary lesion may develop more rapidly, affect the renal pelvis and ureter, and

give the appearance of greater age; also it is quite possible to have a primary hæmatogenous infection of the pyramids or pelvis. As a rule, in experimental hæmatogenous infections the bacteria gather mostly in the glomerular capillaries, going thence into the surrounding tissues, the smaller blood-vessels, or through Bowman's capsule into the uriniferous tubules, as Walker, Bubay, and others have shown. The extreme rarity of primary tuberculosis of the bladder is another argument in favor of the hæmatogenous origin of renal tuberculosis, Kelly having seen but one such case; it must also not be forgotten that if the bladder were the seat of the disease the kidney might be infected from this either by direct extension of the process up the ureter—a less likely mode of infection—or by the blood stream as from any other tuberculous focus; in this latter case this may be either by the general circulation, the vesico-utero-ovariorenal anastomosis or by the bloodvessels of the ureter, and in the later stages of the disease the infection of the second kidney is probably either by this route, or from some other tuberculous focus.

Many authors absolutely deny the possibility of a urogenous infection of the kidney, and Oppel and others claim that it has never been proven. Albarran, however, showed that if tubercle bacilli were injected into the ureter, which was subsequently ligated below the point of injection, renal tuberculosis could develop, and Walker found one case which he believed to be definitely due to this form of infection, this, however, being unique in a series of several hundred experiments. Küster believes that we may get an ascending renal tuberculosis by the development of a tuberculous ureteritis, which subsequently leads to stricture below part, at least, of the infected area, or through antiperistaltic movements of the ureter, which have been observed in cases of vesical tuberculosis. Wildbolz believes that the ascending form is possible although extremely rare; Rovsing is convinced that in 2 of his 56 cases the infection was urogenous; Casper says that the ascending form has rarely been observed in women, but in men it is more common, although much less so than the hæmatogenous form, and sometimes associated with disease of the sexual organs.

The primary source of the infection in these cases often cannot be determined, probably being some infected mediastinal, bronchial, or mesenteric gland, or some slight bone lesion, while in other cases an apical tuberculosis, a cheesy gland, or a tuberculous sinus may be found. Strictly speaking, the disease must always be deuteropathic, even if we are absolutely unable to discover the primary focus, although Israel has described what he believes to be a case of protopathic infection. We must remember in this connection the great tendency of tubercle bacilli to remain latent with decreased virulence in some locality for a considerable period of time, although later the virulence may be increased under a variety of stimuli.

Garceau's figures seem to show that the lungs or the intestinal tract are the most common source of infection in renal tuberculosis, while many observations show that an association has sometimes been noted between renal tuberculosis and tuberculosis of the bones, glands, epididymis, tubes, joints, etc. The fact that most of the figures, however, are from autopsy records must not be forgotten, for here the process has often lost its localized character and become diffuse. Kelynack found the lungs affected in 70 per cent. of his cases of renal tuberculosis, while Flick and Walsh from studies made at the Phipps Institute consider it probable that more than one-half the patients suffering from pulmonary tuberculosis eventually have

tuberculosis of the kidney, and that tubercle bacilli are excreted in the urine in all cases of active tuberculosis, a view concurred in by Heyn from similar studies. In 30 cases of renal tuberculosis, all of which, however, were from autopsy records, that is in the late stage of the disease, the lungs were affected in 28, the abdominal glands in 14, the intestines in 19, the bones in 5, the peritoneum in 5, the spleen in 3, and the liver in 1.

Although many of the figures obtained above are from advanced cases of the disease, it must not be forgotten that infection may be carried from very slight often unrecognizable lesions, that only one kidney may be singled out as the organ to be affected, and that this infection is practically always hæmatogenous.

Accessory Etiological Factors.—In most cases it is impossible to find out any especial predisposing factors, although it is highly probable that at the time of its infection the kidney suffered some lowering of its resistance, possibly due to some transitory cause. Among the predisposing causes which have been described may be mentioned an inherited tendency to tuberculosis, chronic pyelitis, cystitis, and urethritis, gonorrhœa, congenital deformities, especially lobulated kidney, pregnancy, which may produce urinary stasis and renal congestion, floating kidney, cold—frequently mentioned, but extremely doubtful—calculus, hypernephroma, hydronephrosis, trauma, and any conditions which may produce urinary stasis, such as hypertrophy of the prostate, phimosis, and stricture. Trauma was formerly considered a most important factor, but this is hardly born out by modern investigation; thus, in 403 cases Küster found a history of trauma in but 7, in only 2 of which there seemed to be any definite causal relationship between the injury and the infection, while Morpurgo from a series of experiments on rabbits, believes that there is no relationship between trauma and tuberculosis. In floating kidney the lowered resistance is probably due to congestion; Küster found this as the apparent cause in 18 of his 403 cases, and this may be the reason that women are affected more than men, and the right kidney more than the left.

Age.—As regards primary tuberculosis of the kidney practically all authors agree that the commonest age is between twenty and forty years, and the statistics of Casper, Bevan, Morris, Wagner, etc., bear this out. Morris calls attention to the extreme rarity of this condition under ten years of age. Hansen believes that it is met with equal frequency in all the decades beyond the second. In Roberts' series 4 cases were met with in the first decade, 5 in the second, 6 in the third, 9 in the fourth, 9 in the fifth, and 2 in the sixth; in Krönlein's 51 cases, 7 were between seventeen and twenty, 23 in the third decade, 14 in the fourth, 6 in the fifth, and 1 in the sixth. In Morris' 12 cases, 7 were older than thirty years, 5 between eleven and thirty years.

In acute miliary tuberculosis the condition is almost entirely limited to young children, according to Morris under ten years of age in a large percentage of cases. Figures given in this connection, however, show that it is not uncommon in older children and in adults. Cases of primary tuberculosis have been met with in infants a few months old, and in adults over seventy years of age.

Sex.—In regard to primary tuberculosis there is a great divergence of opinion as to which sex is more frequently involved, most of the English writers stating that more cases are found in men, most of the Continental writers more in women. Roberts found 21 cases in men and 12 in women;

Morris, 9 in men and 6 in women. Hansen believes that women and men are affected with equal frequency. All the more modern statistics, however, such as those of Küster, Casper, etc., show that the disease is unquestionably more prevalent in women, Casper stating that it is twice as frequent. Of Krönlein's 51 cases, 38 were women. In acute miliary tuberculosis Morris found, in a series of 29 cases, 18 males and 11 females. Of 46 children under fourteen years of age in Hamill's series, 32 were boys and 12 girls.

Pathology.—The picture is obviously different according to whether we are dealing with an acute miliary tuberculosis of the kidneys or a primary renal tuberculosis, the disease being almost always bilateral in the former, unilateral, at least in the early stage of the disease, in from 90 to 95 per cent. of the latter.

In *acute miliary tuberculosis*, both kidneys show the typical picture of a disseminated tuberculous infection, the tubercles appearing as minute gray nodules usually surrounded by a hyperæmic zone, solitary or grouped together in cortex or medulla, the former being the favorite seat; the nodules are frequently arranged in rows following the course of the interlobular vessels, and often closely resemble small infarctions. Even in this form we may find the infection definitely limited to the areas supplied by one branch of the renal artery. It is not impossible for the bacteria to escape through the glomerular bloodvessels, especially if the walls should be injured, setting up changes in the uriniferous tubules and renal pelvis—Cohnheim's excretion tuberculosis. The changes are most likely to be noted in the interstitial connective tissue, where the characteristic cell proliferation, formation of giant cells, etc., can be seen, with associated degenerative changes in the adjoining parenchyma. Necrosis and caseation are not so common in this form because of the early death of the patient in the majority of cases.

In *primary renal tuberculosis* it is common to make a division along pathological-anatomical lines, according to which portion of the organ is most markedly affected. König describes two forms, the solitary, in which there is no connection with the renal pelvis, and the pyelitic. Israel makes three divisions: phthisis caseosa, frequently associated with perinephritis and paranephritis, and often leading to pyonephrosis; tuberculous ulceration of the points of the papillæ, much less common, but if present associated with a tendency toward severe hemorrhage; and the chronic disseminated tuberculous form, resembling the kidney of acute miliary tuberculosis, except that the disease is unilateral, the tubercles are larger, and the later processes of necrosis and caseation are more likely to be seen. Oppel differentiates cortical and medullary tuberculosis, while Tuffier divides the tuberculous infiltrations of the kidney into three groups—tuberculous pyelonephritis, with or without cold abscess, massive degeneration of the kidney, and tuberculous hydronephrosis.

The pathological picture depends largely upon the duration of the disease, the rapidity with which the changes take place, and the accessory factors. In most cases at a later period the process affects mostly the papillæ and the pyramids, and the pelvis is usually involved, although in some cases the disease is confined entirely to the parenchyma, in rare instances localized in one pole, which, according to Zondek, is due to the fact that it is supplied by a single large branch of the renal artery. Animal experiments and the more recent studies seem to show that in the early stages the medullary

or cortical interstitial connective tissue is most likely to be first affected, the bacilli gathering in the cortical layer, in the Malpighian bodies, or in the capillaries outside the glomeruli, and extending thence as already described. Tubercles may develop in the glomeruli themselves, in the uriniferous tubules, or the renal pelvis, as well as in the interstitial connective tissue; whatever be their situation, infection may be carried secondarily to the papillæ, the pyramids, or the renal pelvis. In the secondary focus the disease may progress more rapidly, while it is possible for the primary focus to show signs of healing; this is one of the reasons why so many renal infections were erroneously regarded as urogenous, and shows how impossible it is to determine the relative age of the process in different portions of the kidney.

The histological changes are the same as in tuberculosis elsewhere: the proliferation of small, round cells, the presence of giant cells, the necrosis, softening, and caseation of the tubercles and their fusion into abscesses of larger or smaller size, with a tendency toward cavity formation, the surrounding renal parenchyma showing cloudy swelling, fatty degeneration, and other degenerative changes of the epithelial cells, leading finally to necrosis and cell death. The formation of new connective tissue tends in some cases to contraction of the kidneys, while, in addition in some cases the typical changes of a chronic interstitial nephritis result, due possibly to attenuated bacilli, possibly to toxins.

The kidney may undergo complete destruction—Tuffier's massive degeneration—due to early ureteral closure by downward extension of the process, and in this form the kidney is usually not much enlarged, if at all, and is represented by a fibrous sac filled with a cheesy, greasy, or calcified mass. When the renal pelvis is involved its mucous membrane is thickened and shows ulceration, the whole surface sometimes being involved; peripyelitis is not uncommon, rarely with perforation into the adjacent tissues. In the various tuberculous foci fresh crops of tubercles may develop by direct extension or by metastasis. If the ureter is more or less impermeable, a pyonephrosis may develop, this being especially likely if there is a secondary infection. A considerable portion of the kidney substance may remain intact, or the organ may be converted into a sacculated mass, the abscesses or cavities being separated by bands or bars of renal tissue; the whole medulla and a large portion of the cortex may be converted into a large cavity, or the kidney may be changed into a shrivelled-up, putty-like mass, due to complete and permanent ureteral closure. Cheesy abscesses, whether large or small, may become inspissated, undergo calcareous change, or be discharged into the renal pelvis, causing a marked and characteristic change in the urine; as a rule, tubercle bacilli are found in these discharges, often in nests or clumps, and sometimes shreds of renal tissue. The kidney, as a rule, is enlarged to a greater or less extent, sometimes considerably so if there is marked obstruction to the flow of urine, and we may have a hydronephrotic or pyonephrotic sac; a polycystic tuberculous kidney has also been described.

Perinephric and paranephric inflammations are quite common in renal tuberculosis, the infection being either by direct extension or by metastasis, the former being the more usual. Sclerotic changes in the fibrous capsule and the surrounding fat may predominate, or we may meet with typical tuberculous changes, abscess, caseation, etc.

Changes in the *ureter* are very frequent, especially in those forms where the renal pelvis is involved, and are almost always present in the later stages of the disease. If ulceration of the mucous membrane of the renal pelvis is present it is likely to extend down the ureter, which is usually dilated in its upper part, while farther down it may become more or less impermeable, due to the inflammatory process. The mucous membrane of the ureter may show fresh tubercles, œdema, swelling and areas of ulceration, while it is not at all uncommon for the peri-ureteral tissues to participate in the inflammatory process; in either case the inflammation may be typically tuberculous, or may be entirely represented by sclerotic changes. In some cases the major portion of the ureter may be unaffected and the diseased process mainly confined to the lower portion, especially the ureteral mouths, which may be of abnormal shape, the surrounding mucous membrane being either reddened or œdematous, or showing definite tuberculous changes. Hallé and Motz, from a careful study of the pathological preparations at the Necker Hospital in Paris, found that the disease was in some instances entirely confined to the ureteral mucous membrane; sometimes ureteritis obliterans was met with and frequently changes in the ureteral mouths and peri-ureteritis. In Roberts' 32 cases of renal tuberculosis the ureters were diseased in 30.

The *bladder* is involved in a large number of cases of renal tuberculosis, although it is surprising for how long a time it may remain unaffected; in the later stages it is practically always diseased. The changes may be limited to the area surrounding the ureteral openings, or may be more extensive, in some cases the entire mucous membrane being involved with ulceration, contraction of the bladder, etc., and associated inflammation of the perivesical tissues. The bladder, although inflamed, may show no typical tuberculous changes, but this is extremely rare. In Roberts' series the bladder was involved in 21 and the urethra in 7 of 32 cases.

The *other kidney* may remain absolutely normal or may be infected from the one primarily diseased, although the second kidney often does not become involved until a long time after the infection of the first. The infection of the second kidney may be metastatic from the diseased kidney, the diseased bladder, or some other focus of tuberculosis, or in rare instances, according to many observers, the infection may arise from the bladder by direct extension through the ureter or by the urogenous route, this latter mode of involvement being denied by many careful observers, and if present unquestionably of extreme rarity. The second kidney may show signs of compensatory hypertrophy, chronic interstitial changes, or amyloid degeneration; Albarran describes the following pathological conditions which may be referable to the other kidney: transitory albuminuria, persistent albuminuria, nephritis, hemorrhagic nephritis, and simple cylindruria.

Unilateral or Bilateral Involvement.—There is, as might be expected, marked discrepancy as to whether the condition is more likely to be bilateral or unilateral, according as the figures are obtained from autopsy records or from clinical observations. In a series of 12,732 autopsies, bilateral involvement was present in 62.3 per cent., unilateral in 37.6 per cent., while in some of the older series, in which obviously the disease was not studied until very late, bilateral involvement was frequent; thus, in Roberts' series of 32 cases, 19 were bilateral, 13 unilateral.

In the more modern clinical statistics, however, there is a marked preponderance of unilateral involvement, showing very definitely that primary

tuberculosis of the kidney in its incipiency or early stages is unilateral in from 80 to 95 per cent. Douglas found this to be 80 per cent.; Bevan, 90 per cent.; Albarran, 91 per cent.; Mirabeau, at least 50 per cent.; Krönlein, 92 per cent.; Israel, 92 per cent.; Kümmell, 88 per cent.; and Facklam, 91 per cent. As regards the frequency of involvement of the two sides, Küster's series of 368 cases showed the right side alone involved 189 times, the left side alone 163 times, both sides 16 times; most figures show this preponderance of the right side, which possibly may be related to the lower position of the right kidney and its greater tendency to descensus.

As regards the frequency of involvement of the kidneys in local and general tuberculosis, the figures differ very markedly, although the frequency after some very slight or even imperceptible lesion is of more interest, as these are the cases which are so susceptible of satisfactory treatment if properly approached. In 6000 autopsies at the Pathological Institute of Prague, 1317 were tuberculous, and of these 5.6 per cent. showed renal involvement; in 3424 autopsies at the Massachusetts General and Boston City Hospitals there were 24 cases of caseous renal tuberculosis; Rillet and Barthez found involvement of the kidneys in 49 of 315 tuberculous children; Dickinson, in 300 autopsies on subjects over twelve years of age, found renal tuberculosis 11 times; in 300 under twelve years of age, 49 times; in 2410 autopsies at the Middlesex Hospital there were 29 cases of miliary and 15 of primary renal tuberculosis. According to Wagner, surgical or primary renal tuberculosis is present in about 10 per cent. of all cases of tuberculosis. The proportion of cases which show renal involvement should in all probability be larger than those given in the figures above, in which the main dependence was upon the macroscopic appearance of the kidneys. This is also suggested by the work of Flick and Walsh at the Phipps Institute, Philadelphia, who showed that in practically all cases of advanced pulmonary tuberculosis, tuberculous lesions of the kidney could be found, although sometimes very slight and only made out by microscopic study.

Before leaving the subject it is of interest to call attention to some of the recent work on experimental tuberculosis of the kidneys in animals, as these throw a great deal of light upon our conception of the disease, especially as regards the early stage. Jossuet showed that inoculation of tubercle bacilli into the rabbit's artery would usually cause renal tuberculosis, especially if the kidney's resistance was lowered by the administration of some toxic substance. Tuberculous deposits followed the arterioles and were frequently limited to the cortical region, the deposit in the medulla being dependent upon a secondary lymphatic infection from this primary focus. Besides this specific change, he found parenchymatous or interstitial nephritis, congestion, hemorrhage, leukocytic infiltration, or amyloid degeneration, these changes, according to Jossuet, being due to the microörganism itself rather than to its toxins. It is also possible to have a tubercle bacillus bacilluria with slight albuminuria, probably due to a transitory nephritis of mild grade.

Bernhard and Salomon found that with the toxins produced by the tubercle bacillus fibrous changes and an accumulation of leukocytes could be produced; after injecting the tubercle bacilli into the bladder and ligating the ureter no renal tuberculosis was noted by them, although if the injection was into the renal pelvis and the ureter was tied tuberculosis developed. Bubay, after injecting virulent tubercle bacilli into the carotid and renal

arteries, found that the first groups of bacilli were to be met with in the dilated glomerular loops, about which was gathered a homogenous mass of multinuclear leukocytes, and on the second day large cells with vesicular nuclei, probably phagocytes, while Walker found that the bacteria gathered mostly in the glomerular vessels, going thence into the surrounding tissue, into the smaller bloodvessels or through Bowman's capsule into the uriniferous tubules.

Symptoms.—*In acute miliary renal tuberculosis* characteristic symptoms referable to the kidney are rarely present; oliguria and albuminuria may be due to renal involvement or be but a sign of general infection; tubercle bacilli, although usually found if carefully looked for, may not be indicative of any marked involvement of the kidneys, as they are found in the urine in most cases of general miliary tuberculosis and advanced phthisis, Flick and Walsh finding them in 44 of 60 cases of the latter disease; lumbar pain may be complained of, but this is not uncommon in general infection. As, however, the renal disease is but a part of a general miliary infection, or appears as a terminal infection in severe lesions elsewhere, our inability to determine from the symptoms whether the kidney is or is not involved is of very little moment.

In chronic or primary renal tuberculosis the conditions are very different, the whole future of the case depending upon a prompt and clear recognition of the symptoms. Unfortunately symptoms referable to the kidney may be absolutely wanting at first, the patient only making complaint when the bladder becomes involved or the constitutional disturbances are very evident.

The clinical course of renal tuberculosis may be divided into four stages: (1) The latent stage; (2) from the involvement of the pyramids to the infection of the bladder; (3) the stage of bladder involvement; and (4) that of the infection of the other kidney. In the later stages diagnosis, as a rule, should not be difficult, but a successful issue depends on our being able to make an early, not a late diagnosis, and it is, therefore, the early symptoms that are especially important; in the majority of cases careful questioning and a thorough investigation will reveal some symptoms suggestive of renal disease. It is possible, however, for the disease to run an absolutely silent course, even until the kidney is completely destroyed, while the length of the latent period depends upon whether the involvement of the renal pelvis is early or late; even in marked disease of the cortex there may be no symptoms whatsoever. As seen clinically the first symptoms, both objective and subjective, are usually referable to the bladder, and are often difficult to interpret properly; many cases for a long time have been regarded as simple cystitis or irritable bladder.

The most important symptoms are: (1) Changes in the urine, both as regards its flow and its physical, chemical, and microscopic constitution; (2) local swelling and pain; (3) constitutional disturbances. The first of these in the majority of cases is by far the most important in arriving at an early diagnosis.

1. **Urine.**—The first symptoms are usually disturbances of urination; there is an increased frequency, with burning, sometimes cramp-like pains, usually beginning about the middle of the flow, increasing to the end, and ceasing with the complete emptying of the bladder. This increased frequency is especially likely to be present at night, and may be due to a reflex stimulation of the bladder, an associated cystitis, or perhaps excessive acidity of

the urine. As a rule, although not always, these disturbances are not severe except when the bladder is involved, when they may assume the most painful proportions, strangury, dysuria, and frequency of urination sometimes reaching an almost incredible degree, torturing the patient day and night and making life unbearable. Incontinence is seen in a few cases, and Bazy regards this if present as a very important early symptom. The frequency may be constant or intermittent, and with the pain may unquestionably precede the involvement of the bladder by a considerable period of time. For this reason it is probably the most important symptom, as it calls attention to the urine and suggests the advisability of making a careful examination. Roberts reports a patient voiding on an average 160 times daily, in whom the bladder, however, was but slightly diseased; in another micturition was incessant until nephrotomy with drainage was performed. In some cases, even before the increased frequency and pain, the patient notices a constant or intermittent cloudiness of the urine.

The *amount* of urine varies markedly; according to some it may be diminished at first, while according to Guyon, Tilden Brown, and others, polyuria is a cardinal early symptom, especially nocturnal polyuria; in many cases the amount is practically normal. In the later stages the amount may be normal, diminished, or even increased according to the extent of destruction of the kidney tissue and the degree of hypertrophy of the sound kidney. When both sides are extensively involved, or when the flow from the diseased side ceases, due to stoppage in the ureter, we may have oliguria or even anuria. If both kidneys are catheterized, it is interesting to note the larger amount from the normal kidney, and its much quicker and more marked response to the taking of fluids by mouth. Küster has shown that in rare instances a polyuria may develop in the later stages of the disease if the ureter on the diseased side suddenly becomes closed, the urine being clear under these circumstances if the bladder is not involved; polyuria with cloudy urine, although sometimes met with in the later stages of the disease, is extremely rare.

The *reaction* is always acid unless the disease is complicated by an alkaline cystitis or pyelitis, or unless the patient is taking large quantities of alkalies. In some cases the acidity is increased. If there is an associated infection with one of the urea-decomposing bacteria the odor may be very foul, this being more likely to occur in the later stages of the disease.

The *albumin* present varies considerably in amount. It is usually small in the early stages, corresponding to the amount of blood and pus present, while later it is likely to be increased because of the frequent presence of an associated interstitial or parenchymatous nephritis in other portions of the diseased kidney. If the specimen is obtained directly from the diseased kidney, even in fairly early cases, a moderate or considerable amount of albumin is the rule, the smallness of the amount in the specimen from the bladder being due to its admixture with a much larger amount of clear urine from the normal kidney. The urine from the other kidney may sometimes contain albumin even without tuberculous disease, due, as a rule, to transitory toxic changes, the albumin often disappearing rapidly after removal of the diseased organ.

The urine may be absolutely clear, as, for example, when the ureter is temporarily blocked or permanently closed, or when the disease is entirely confined to the cortex; the examination of the sediment, however, is of the

utmost importance, and, as a rule, it is the finding of pus cells, often red blood cells, and tubercle bacilli in the sediment from the cloudy specimen of urine that gives the diagnosis.

The presence of *tubercle bacilli* is of the utmost importance, and, excepting in cases of general miliary tuberculosis or an active tuberculous process elsewhere, it is the most important diagnostic sign of primary renal tuberculosis. They may be found in the great majority of cases if the sediment obtained from a considerable amount of urine is centrifugalized and repeated examinations are made, preferably at intervals of several days. They are rarely present in large numbers, and often require very careful searching of many specimens; if the bladder is involved they are usually found with greater ease, although even here time and patience are required. Nests or clumps of the bacilli are often found embedded in the masses of pus, crumbling caseous material, necrotic tissue, and detritus which are present in the urine when an abscess ruptures into the renal pelvis. In 195 cases collected by Küster in which tubercle bacilli were searched for, they were found in 94, not found in 101, although unquestionably with greater care and persistence they could be found in a far larger proportion.

Pus cells are almost always present, although in varying amount; it is sometimes the cloudiness of the urine which first calls the patient's attention to his trouble. Pyuria is usually more marked if the renal pelvis is involved, and especially if there is an associated tuberculous cystitis, or a mixed infection, while it is not at all uncommon for the urine to become suddenly thick with pus after the rupture of an abscess into the renal pelvis. Ebstein believes that the pus cells are very likely to be abnormal, irregular in outline, broken up, and with indistinct nuclei. If there is an associated alkaline cystitis, the pus cells, red blood cells, and mucus may appear as a thick, viscid mass.

Blood in the urine is a very important symptom of renal tuberculosis, microscopic blood being found in the great majority of cases and macroscopic blood not uncommonly. Red blood cells are peculiarly likely to be present in the early stages, and a macroscopic hæmaturia may be the first sign noted. Macroscopic hæmaturia is usually intermittent, rarely profuse, as a rule not affected by rest or exercise, and associated with pyuria usually of moderate grade. According to Casper, hemorrhage is more likely to occur in the early stage, as the progression of the disease is associated with increasing obliteration of the bloodvessels. Tuffier, Albarran, Pousson, and others have reported cases of severe bleeding, requiring immediate operation, in renal tuberculosis, while more recently Askanazy has reported five cases of his own and a number from the literature in which more or less marked macroscopic hæmaturia recurring at intervals was the earliest symptom, usually coming on suddenly and in some cases being the only sign of disease for many years; in one case sixteen, in another thirteen years elapsed before other symptoms appeared. The blood may sometimes entirely stop up the ureter, producing colicky pains, which often disappear with the appearance of worm-like blood clots in the urine—blood casts of the ureter. In patients operated upon Askanazy found either tuberculous ulceration of the apices of the papillæ, or of the renal pelvis, or in some cases simply a scattered miliary tuberculosis; in these latter cases he believes that the hemorrhage is due to an acute arterial congestion of the kidney which is likely to be associated with colicky pains; Klebs believes that these early hemorrhages may

be due to an angiotoxin produced in the growth of the bacteria in the body. Cases have been reported in which ulceration of only one papilla has caused such severe hemorrhage as to require immediate operation.

Epithelial cells from the renal pelvis, ureter, or bladder are usually present and may show signs of fatty degeneration. *Casts* were found by Hunner in 10 per cent. of his cases, although, according to others, both hyaline and granular casts are found much more frequently than this. Their presence is due to an associated nephritis in the diseased kidney as a rule, but they may come exceptionally from the other kidney, which, as Albarran has shown, may be affected by the circulating toxins. Granular amorphous masses, crumbling cheesy material, bits of kidney tissue, masses of friable detritus, often with tubercle bacilli embedded therein, fibrous tissue, and elastic fibers are occasionally found, and when present are of great diagnostic value; fragments of stone may be noted if renal calculus and tuberculosis are present together, but this is a rare association.

2. **Local Swelling and Pain.**—Local swelling is an important but inconstant symptom, although in the later stages it may often be made out, or at least a feeling of increased resistance or of distention to the palpating hand, the organ frequently being less movable than in health. The presence of perinephritis or paranephritis increases markedly the chance of finding a palpable tumor. The local swelling is usually not very marked except when associated with pyonephrosis, hydronephrosis, or paranephric abscess; the largest tumors are those due to a pyonephrosis with mixed infection, and in these cases it is not uncommon to find changes in the size of the tumor due to changes in the ureter, while occasionally the soft walls of the cavities can be made out, especially if the patient is much emaciated. Roberts found a distinct tumor in 7 of his 35 cases, but seldom of great extent, while von Ammon reports a case in which the swelling extended from the false ribs to the crest of the ilium. Usually at operation some increase in the size of the kidney is found, although a diminution is sometimes met with.

Local pain, frequently absent or slight in the early stages of the disease, may occur spontaneously or may only be elicited by pressure, the former being, as a rule, more a dull ache, a sensation of fulness, dragging or pressure, or a sense of soreness than a severe pain. This is usually due to stretching of the capsule, and may radiate to the bladder or thigh. The pain may be constant and paroxysmal, and increased by exercise, while in addition we sometimes meet with cases of typical renal colic due either to occlusion of the ureter with detritus, blood, etc., or to acute arterial congestion, the latter, associated with hæmaturia, being an important early symptom in a small proportion of cases. Tuffier's *forme douloureuse* with neuralgic pains in the renal region is extremely rare. Bazy finds three points where pain may be produced by pressure, para-umbilical, subcostal, and lumbar, while pain and tenderness in the costovertebral triangle is common if there is much perinephric or paranephric involvement, this latter being often associated with swelling, fever, and severe constitutional disturbances. It must not be forgotten that in some cases the pain, as well as the swelling, is referred to the healthy kidney which has undergone compensatory hypertrophy.

3. **Constitutional Disturbances.**—Constitutional disturbances are usually present, although, as a rule, not marked until fairly late in the disease. It is not uncommon to find a gradual impairment of the general health, dimin-

ishing strength, fatigue on slight exertion, and unaccountable dyspnœa. In other cases, but these are rare, the constitutional symptoms may develop rapidly and the picture resemble typhoid fever; such a resemblance is not uncommon in the later stages. As a rule, the constitutional disturbances develop gradually, while in some cases the condition may persist for a long time, with no apparent impairment of the general health. In the later stages the constitutional symptoms are marked—emaciation, anæmia, cachexia, anorexia, and other digestive disturbances, fever, chills, and profuse sweats. These symptoms are usually more severe and develop more rapidly if the bladder becomes involved, or if there are signs of active tuberculosis elsewhere, and it is always important to determine whether some of the symptoms at least are not referable to an active lesion outside the urinary tract. If the bladder is markedly involved, the constant and severe pain, the incessant frequency of urination, and the loss of sleep may cause rapid emaciation and marked depression, both mental and physical. In rare instances primary renal tuberculosis may develop with the typical symptoms of acute nephritis, œdema, nausea, vomiting, oliguria, etc.; œdema may also be present in the later stages, especially if both kidneys are involved.

Fever is present in a fair proportion of the cases, although often absent during the latent stage. According to Israel fever is present in only 22 per cent. of the cases of uncomplicated renal tuberculosis, and in 80 per cent. if the bladder is also involved, but these figures, especially the former, are too low. In the early stages fever, if present, is likely to consist simply of a regular or intermittent evening rise of one or several degrees, while in the late stages, especially if associated with marked bladder involvement, it is usually irregularly intermittent, remittent, constant, or of the hectic type, in this latter instance profuse sweats being a common accompaniment, especially night sweats, while in some cases frequent chills are met with. The more constant and the higher the temperature the more rapid the development of the general symptoms, emaciation, digestive disturbances, anæmia, etc.

Digestive disturbances are frequent in the later stages, while diminution of appetite is a not uncommon early symptom. In advanced cases marked gastro-intestinal disturbances are common, such as diarrhœa, persistent or alternating with constipation, marked anorexia, etc., while von Ammon has reported a case in which there was a marked temporary bulimia.

The pulse is rapid if nephritis is present or in advanced cases, its rate otherwise being dependent upon the degree of fever. Reitter believes that hypotension of the pulse is a differential symptom of great importance, as he found it in 6 of 10 cases of renal tuberculosis even with marked evidences of nephritis.

Anæmia, oligæmia, oligochromæmia, or oligocythæmia is present in all advanced cases, and may appear rather early; in uncomplicated cases the leukocytes, as a rule, are either normal or diminished, the neutrophiles being especially reduced, while if there is a secondary infection, leukocytosis is the rule. If both kidneys are markedly diseased, the freezing point of the blood may be less than —0.6° C.

Course.—As acute disseminated renal tuberculosis is but a part of an acute general tuberculous infection, the course is rapid and the termination always fatal.

The course of primary renal tuberculosis is chronic and may last months

and even years; the disease, while progressive, often develops so slowly that no changes may be noted in long periods of time. The difficulty or inability of determining the exact beginning of the disease makes it impossible to tell the exact duration, but from the first appearance of the symptoms to the end, five or more years may elapse, and in some cases symptoms have been present for more than ten years; in one-half of Krönlein's cases the symptoms had been present one year, in the other half two to four years or longer, while in Kelly's group of 62 cases the average duration was three and a half years, one patient having had definite symptoms for thirteen years, yet showing on operation some secreting tissue still left in the diseased kidney, and the other kidney normal. He noted the long period of time which elapsed, as a rule, before the involvement of the second kidney, and in some cases even of the bladder. There is often a considerable fluctuation in the symptoms, not infrequently even a marked improvement, and then a gradual or rapid progression. Usually an increase in the local symptoms brings about a corresponding increase in the general symptoms and hastens the end. A number of complications may occur; the perinephric and paranephric tissues frequently show involvement, often associated with increased pain, swelling, and severe constitutional disturbances, while disease of the ureter and bladder is extremely common; the other kidney may show toxic changes, a simple pyelitis, or typical tuberculosis; the picture may be confused by the development of a ureterovaginal or vesicovaginal fistula, while by metastasis or direct extension the nearby and distant organs may be involved in the tuberculous process, or the cheesy abscesses may rupture externally or into the neighboring organs.

The *cause of death* in chronic renal tuberculosis may be exhaustion or septicæmia, the latter being especially likely to occur if the paranephric tissues are extensively diseased, or if there is a severe mixed infection; metastasis and general dissemination of the tubercle bacilli; metastatic tuberculosis of other organs, as most commonly the lungs, the intestines, the peritoneum, etc.; amyloid disease; extension of the disease to the tissues surrounding the kidney, with abscess formation and subsequent rupture, and in very rare instances uræmia, the latter occurring when both kidneys are diseased, or in some cases when one is removed and the other is tuberculous, shows signs of nephritis, or is absent altogether.

Diagnosis.—The realization that renal tuberculosis is usually unilateral, that its origin is almost exclusively hæmatogenous, and that it is a disease very susceptible to treatment if recognized early, makes the necessity of a prompt and correct diagnosis of the utmost importance; in fact, if a cure is to be hoped for, early diagnosis is absolutely essential. If the diagnosis is easy it is usually because the disease is far advanced and often beyond the possibility of successful treatment, while to make an early diagnosis always requires careful and often repeated examinations, the use of the modern instruments of precision, and thorough study. It is important that we should make the diagnosis, if possible, before the appearance of marked constitutional symptoms and involvement of the bladder. This may be extremely difficult from the quiet afebrile course of the latent stage and its marked freedom from striking symptoms. It is necessary to consider carefully the family history, the past history, the general appearance of the patient, the presence of pain, dysuria, polyuria, hæmaturia, increased frequency of micturition, etc., to examine the urine thoroughly, to use the cystoscope and

ureteral catheter, to make careful bacteriological studies, and in some cases to give tuberculin.

It is a good practice to look for tubercle bacilli in every acid, sterile, purulent urine, and to suspect renal tuberculosis in cases of slight urinary disturbances or constitutional disturbances with no apparent cause. Physicians should pay more attention to complaints of lumbar pain localized in one side and persisting for some time; the possibility of renal tuberculosis should be considered in all febrile cases, especially those characterized by an evening rise of temperature; all cases of cystitis not yielding to treatment should be investigated in this connection, and every case of cloudy urine with no bladder symptoms, especially if associated with signs of tuberculosis elsewhere; the possibility of a tuberculous origin should be remembered in every case of renal hæmaturia without definite cause. It must not be forgotten that chronic gonorrhœa, renal calculus, or neoplasm may be associated with tuberculosis, and the discovery of the former does not necessarily exclude the latter; that in some cases the classical symptoms may be lacking, there may be no pain, no swelling, no general disturbance, and even, temporarily at least, no changes in the urine, and that it is only by repeated examinations and the careful weighing of every symptom and sign in these cases that a diagnosis can be made. To make a positive diagnosis tubercle bacilli must be found in the urine, and proved to have arisen from the kidney, while if this is not possible a presumptive diagnosis may be often made from the local pain and swelling, sterile renal pyuria, renal hæmaturia, and tuberculous lesions elsewhere in the body, although it must not be forgotten that the pain and swelling may be referred to the healthy kidney. If renal tuberculosis is diagnosed it is well to look for tuberculous lesions elsewhere and determine if possible the primary source of the renal infection. In the later stages the diagnosis is often very easy, the patient shows signs of tuberculosis elsewhere, the kidney is painful and swollen, and the urine contains pus cells and tubercle bacilli, but no patient should be allowed to reach this stage and none need if the possibility of renal tuberculosis being the cause of clinical pictures of doubtful etiology and vague symptoms, referable in the majority of cases to the urinary system, is kept constantly in mind.

The study of the urine gives, as a rule, the most important signs, pyuria, hæmaturia, and the finding of tubercle bacilli giving the diagnosis in the majority of cases. The urine should be obtained by catheter to avoid contamination with the smegma bacillus, while, whenever possible, separate specimens should be obtained by the ureteral catheter. The urine should be studied with especial care when increased frequency, especially nocturnal, and pain on urination have been noted, and also, according to many clinicians, in cases of polyuria with no apparent cause. Red blood cells are usually present, although often only demonstrable microscopically, while macroscopic hæmaturia is often very abrupt in both its onset and its disappearance, and may occur intermittently.

Pyuria is usually present and of great importance, and every pyuria in an acid urine which shows no growth on the ordinary media should be investigated with great care. According to Ebstein, Colombino, and Moscou, abnormalities of the pus cells are found more commonly in renal tuberculosis than in other conditions, and irregular broken-up forms with indistinct nuclei are frequently met.

The finding of *tubercle bacilli* in the urine gives the diagnosis if proven to be derived from the kidney, which is easy when ureteral catheterization is possible; we must not forget that they are commonly met with in the urine, however, in the case of active tuberculosis elsewhere. If the urine is obtained by ureteral or urethral catheterization the ordinary means of staining and studying the bacteria are all that is necessary, but if voided specimens are examined the tubercle bacillus must be differentiated from the smegma bacillus, and this may be done either by animal inoculation or by certain staining methods, such as those of Bunge, Trantenroth, and Dahms. Ekehorn found tubercle bacilli in every one of his 55 cases by careful search, although according to Casper they can be found in but 70 to 80 per cent. of all cases. Personal experience agrees with that of Ekehorn, although it is often necessary to make frequent examinations of the centrifugalized sediment. In suspicious cases where they are not found, guinea-pigs should be inoculated with the sediment, and, if it contains tubercle bacilli, in from four to six weeks definite tuberculous lesions will develop. Bloch and others have suggested that to make an earlier diagnosis by this method, certain of the lymph glands be bruised or injured, as they found that under these circumstances definite tuberculous changes may be noted in nine or ten days.

Functional tests of the urine from the separate kidneys should always be made when possible, although it is well to remember that a tuberculous kidney may give absolutely normal readings. If the disease is advanced, however, the figures from that kidney in the great majority of cases are low, and these are of especial value in cases where operation is under discussion, although a great majority of surgeons lay more stress upon the microscopic and bacteriological findings than upon these functional tests. Some clinicians lay great stress upon blood cryoscopy as a means of determining whether one or both kidneys are diseased, but this in the main is unreliable.

The use of the cystoscope and the ureteral catheter has revolutionized the diagnoses of renal diseases. By *cystoscopy* we can determine whether the bladder is involved, and the character and extent of the disease, while by studying the condition of the ureteral openings and the contiguous mucous membrane the unilateral or bilateral character of the disease may be determined with a fair degree of accuracy, this being greatly helped by watching the character of the urine flowing from each ureteral orifice; in some cases this urine may be caught in the cystoscope and studied subsequently. A dislocated, retracted ureteral mouth surrounded by reddened or swollen mucous membrane or by distinct ulcerations is very suggestive of tuberculous disease of the corresponding kidney, especially if the bladder shows slight involvement elsewhere. A cloudy or bloody urine from one ureteral orifice will often give the diagnosis, while the functional ability of the two sides may be gauged to a certain extent by the relative amounts flowing from each; if the bladder is much diseased, chromocystoscopy is of great value in helping us to find the ureteral orifices. Cystoscopy sometimes fails, as in the case of very painful contracted bladder, extensive swelling of the vesical mucous membrane, and profuse bleeding on instrumentation.

The ureteral catheter should be used if possible in every doubtful case, for if used with care the procedure is practically devoid of danger if the bladder is carefully washed out, the ureteral orifices swabbed off, the technique most rigid, the patient given considerable water before the procedure, and the catheter introduced but a short distance until the condition of the

two sides is determined. Albarran and Nitze shut off the diseased side with a large catheter, and thus obtain urine from the other side without catheterizing its ureter, but this is only of value when the bladder is not involved. There is frequently considerable difficulty in introducing the catheter into the diseased side, while if definite ureteral stricture is present considerable force may be necessary, the finding of such a stricture being a very important sign of renal disease. By means of the ureteral catheter the presence of the two kidneys can be verified, and the urine from the two sides studied separately.

An exploratory nephrotomy may be necessary if the cystoscope and ureteral catheter cannot be used, but the results obtained thereby are by no means so definite.

The *x*-rays are sometimes helpful in showing that the kidney is enlarged or thickened, although of more value in the differentiation of renal tuberculosis from calculus. The tuberculous kidney often gives a deeper shadow than the normal organ, while if abscesses and cavities are present the shadow may show marked variations.

The finding of a *thickened ureter* by vaginal examination is of the utmost diagnostic importance, as it is much more frequently met with in tuberculosis than in any other renal lesion.

Tuberculin may often be employed in doubtful cases, the subcutaneous method being more satisfactory than the ophthalmic or skin reaction or the methods by suppository or inunction. Most clinicians are agreed that if properly given this method is practically devoid of danger. It is not only necessary to obtain a febrile reaction to diagnose renal tuberculosis, but in addition there must be pain or increase of pain in the kidney region, or an increase of the pus cells, red blood cells, and tubercle bacilli in the urine, which sometimes completely changes in appearance after a tuberculin injection. In advanced cases, especially if the dose is large, the injection may be followed by anuria and serious consequences, although this is not common. Czerny reports a case in which after the injection the pain and swelling increased in the kidney region, while for one day the urine was absolutely clear, probably due to shutting off of the ureter, and then there was a marked increase in the pus cells and tubercle bacilli, while Birnbaum has reported 100 cases in which the tuberculin findings corresponded with the clinical course of the disease. Froment has recently reported 100 cases in which the agglutination test of Arloing and Courmont was used successfully. As in all cases of renal tuberculosis there is some focus, albeit a small one, of the disease elsewhere, it is necessary to obtain a local as well as a febrile reaction to confirm the diagnosis.

Differential Diagnosis.—The conditions for which renal tuberculosis may be mistaken are pyelitis, pyelonephritis, empyema of the renal pelvis, calculus, renal cancer, hypernephroma, cystic kidney, and essential hæmaturia. Renal cancer and calculus are most likely to cause confusion, while it must not be forgotten that in some cases these diseases and tuberculosis may co-exist. *In calculus*, pyuria, as a rule, develops slowly, colic is frequent and usually severe, the pain extending down the ureter and being associated with profuse sweats; a frequent, scanty, high-colored, scalding urine, with gritty particles, is passed sometimes after the attack; usually there is no evening rise of temperature, and the general nutrition is well preserved, while the hæmaturia and pain are lessened by the recumbent position and are usually

intermittent. The *x*-rays and the wax-tipped catheter may definitely decide the diagnosis. In *malignant tumors* of the kidney or its pelvis the bleeding is often profuse, with no apparent cause, and with a marked tendency to intermit; the urine is often normal, pyuria being far less common than in tuberculosis; pain is unusual, swelling is common, while in the later stages cachexia is present. *Pyelitis* or *pyelonephritis* due to the pyogenic bacteria may occasionally simulate renal tuberculosis, but the presence of the bacteria and, in the cases with marked suppuration, the higher fever and more severe constitutional symptoms should make the diagnosis easy in most cases. The possibility of *hypernephroma* must not be forgotten if the *x*-rays and bacteriological examination are negative and tumor is present.

In renal tuberculosis the pyuria develops early, and is in most cases constantly present; an evening rise of temperature, chills, sweats, loss of appetite, and some emaciation may be met with; blood is usually present in the urine, although rarely in large amounts, while macroscopic hæmaturia is generally intermittent and, as a rule, not affected by exercise; tubercle bacilli can usually be found by careful searching, and there are often evidences of tuberculosis elsewhere; typical renal colic is sometimes present; the urination is often frequent and burning, especially at night, while according to some the amount is frequently increased. *Hæmaturia* without pain may also be met with in chronic interstitial nephritis, renal angioma, floating kidney, hydronephrosis, certain tropical diseases, and from no apparent cause the so-called idiopathic or essential hæmaturia. In urethral hæmaturia the urine is usually bloody at first and later clear, in vesical hæmaturia clear or lightly tinged, and then progressively darker, while in renal hæmaturia the urine, as a rule, is uniformly colored; the source of the blood cannot be determined definitely by these means, however, but only by the use of the cystoscope and the ureteral catheter. Great vesical tenesmus with marked increase in the frequency of urination points to cystitis, but this does not exclude renal disease.

Ureteral thickening due to extension down the ureter is frequently met with in renal tuberculosis, and can usually be made out in women by vaginal palpation. In uncomplicated tuberculosis *leukopenia* is the rule, while in all septic processes due to mixed infection leukocytosis is usually met with. Anæmia is more common in renal cancer and tuberculosis than in calculus. The low blood pressure described in renal tuberculosis may help in making a differential diagnosis.

The differential diagnosis may usually be made by a consideration of the above factors, by a careful history and thorough physical examination, by the use of the cystoscope and ureteral catheter, and by thorough examination of the urine, but in a few instances it is impossible to definitely decide whether we are dealing with renal tuberculosis, malignant disease, calculus, purulent pyelitis, or pyelonephritis; fortunately in all these cases the treatment is the same.

Prognosis.—This depends on a large number of factors; upon whether operation is or is not performed; upon the stage of the disease, whether it is unilateral or bilateral, whether the ureter and bladder are involved, and whether there is any active tuberculosis elsewhere; the prime requisite for a favorable prognosis is an early diagnosis. The prognosis is unfavorable if the disease is let alone, although there is some discussion regarding the

advisability of immediate operation in very early stages. Pathological anatomy shows that healing may occur spontaneously, although Küster has been able to find but one case where a spontaneous cure could be proven clinically. In rare instances the kidney may be completely destroyed and remain encapsulated, although it is hard to see how this can fail to be a source of danger as regards secondary infection. Several writers have reported spontaneous recoveries, and Godlee and others insist that if climatic and hygienic treatment were tried in the early cases a number would be definitely cured. Albarran, however, denies that a spontaneous cure has ever taken place, and Kelly has never seen a medical cure, although in a number of early cases he tried rest, forced feeding, fresh air, etc., for a number of months.

The exact status of tuberculin therapy has not yet been determined, but if it should prove successful, early renal tuberculosis should prove a useful field for this mode of treatment. At the present writing, however, it seems that as the prognosis is unfavorable if let alone, as cure is improbable under general hygienic treatment, and as the chances of recovery are so much lessened by delay, early operation is *the treatment* for chronic renal tuberculosis, if we can determine definitely the presence, the functional ability, and the freedom from disease of the other kidney and the absence of extensive tuberculosis elsewhere. It is beyond question that operation in many cases may restore the patient's health and in others may prolong life; but we must not forget that this form of renal disease is always secondary, and that even after its removal the patient for a considerable period of time should be carefully treated in the hope that the primary focus may become entirely healed. The results of the operative treatment will be considered in the section on treatment, but it is surprising in how many cases bladder tuberculosis, which was formerly regarded as a distinct contra-indication to operation, is susceptible of successful treatment after the removal of the diseased kidney. It is always well before giving a prognosis to look carefully for signs of tuberculosis elsewhere, especially in the lungs and the other kidney, for the successful issue in every case depends upon the surgeon's ability to remove most, if not all, of the active foci, and to leave an organ capable of carrying on the renal function.

Treatment.—The general *prophylaxis* is the same as in tuberculosis elsewhere—fresh air, sunshine, good food, keeping the nutrition of the body at its highest point, and lessening as far as possible the chance of exposure to the germs of tuberculosis. If tuberculosis should be present in the body it should be treated as early as possible along the approved lines. The special prophylaxis consists in removing if possible any focus of tuberculosis that may be present in the body, in the epididymis, glands, joints, bones, etc., and to obviate as far as possible all conditions which tend to lower the resistance of the kidney, especially diseases of the urethra, prostate, and bladder, gonorrhœa, nephroptosis, etc. The rules for general and special prophylaxis are especially referable to those with a tuberculous family history or to those peculiarly liable to exposure to tuberculous infection.

Our views regarding the *treatment* of primary renal tuberculosis have undergone a marked change during the past twenty years. In 1885 Fisher condemned nephrectomy in renal tuberculosis, and shortly afterward von Volkmann stated that he doubted whether operation had any real value in this disease; in 1890 Madelung recommended nephrectomy only in advanced

cases, "when the disease has progressed so far that spontaneous recovery is impossible."

The present attitude of the great majority of physicians and surgeons regarding renal tuberculosis is that in the vast majority of cases surgical treatment offers the only hope of real cure, and that the earlier this treatment is inaugurated the better the chance of recovery. It is beyond question that at the stage in which the disease is usually recognized the condition will advance under any other form of treatment, and it is only those cases in which an extremely early diagnosis is made in which general treatment would be at all justifiable. We realize that amyloid disease or toxic nephritis of the other kidney will render the prognosis much less favorable, and will usually preclude operative treatment, and it is therefore important to remove the source of the toxins before such changes occur, while the longer the operation is postponed the greater the chance of a more general tuberculosis and the less the chance of recovery when operation is performed. The older view was that active tuberculosis elsewhere, especially in the lungs and the bladder, was a distinct contra-indication to operation, but more recent work has shown that in the case of the latter even extensive disease is no bar to nephrectomy, while in the case of the former, although, as a rule, an advanced active lesion would preclude operation, yet in a number of less active and not so advanced cases distinct improvement may follow the removal of the kidney. If the symptoms referable to the kidney and bladder are very marked, and the pain, tenesmus, increased frequency of urination and constitutional disturbances are making life a burden to the patient, it is justifiable even in advanced cases to take some risk in the hope of ameliorating the condition.

In the very early cases the last word has not been said, and with the means at hand of making an earlier diagnosis the next few years should determine what effect climatic, hygienic, and dietetic treatment and the therapeutic use of tuberculin will have; at present, in the majority of cases, such treatment has not been successful, although in some at least this may have been due to the fact that the treatment was not started until the disease was too far advanced. In the most advanced cases operative treatment may be out of the question and symptomatic treatment alone justifiable, as, for example, when the other kidney is considerably diseased or when there is extensive tuberculosis elsewhere.

Surgical Treatment.—All physicians are agreed that primary *advanced* renal tuberculosis should be treated by nephrectomy if the other kidney is healthy, and if tuberculosis is not too far advanced elsewhere, while in the treatment of the early stages there is still some difference of opinion, Tuffier, Guyon, Israel, Legueu, and some other physicians and surgeons believing that medical, hygienic, and dietetic treatment should be tried, while Rovsing, Casper, Küster, Wagner, and the great majority believe that no case is too early for operative treatment. It would certainly seem unwise to wait until the general health has suffered and symptoms of the advanced disease have made their appearance, with the extreme improbability of bringing about a cure by medical treatment alone.

The operations which may be considered are nephrectomy, nephrotomy, nephrostomy, and partial resection of the kidney, although the first of these is always the operation of choice if the circumstances warrant it, that is if the other kidney is healthy and the general condition of the patient is such as to warrant the operation.

In *nephrectomy* it is, of course, of paramount importance that the presence and healthy condition of the other kidney be determined. According to Rovsing, the absence of albumin, pus, or bacteria from the second kidney may be relied upon as a rule; if pus and bacteria are present, removal of the first kidney is usually contra-indicated, while if albumin but no pus or bacteria is found, it is not a contra-indication, the albuminuria being due to toxic changes and usually disappearing rapidly after the removal of the diseased organ. The functional tests, while by no means so valuable as the examination for tubercle bacilli, pus cells, red blood cells, and albumin, are of help, especially if positive, the most reliable being the urea, phloridzin, and cryoscopic tests and the dilution experiment.

Kümmel divides renal tuberculosis into three groups surgically speaking: (1) The early stage, where operation can be done; (2) when one kidney is severely and the other slightly diseased, and here, according to Kümmel, if the freezing point of the blood is —0.56° to —0.57° C., the more seriously diseased organ may be removed, while if —0.6°C., nephrotomy must be done; (3) where the ureteral catheter cannot be used, and here an exploratory nephrotomy should be done, and from the findings and the cryoscopic index of the blood the proper treatment can be decided upon. Most surgeons do not rely on the blood cryoscopy as Kümmel does, and determine the condition of the kidneys by other means when cystoscopy and ureteral catheterization cannot be employed, sometimes even by a double exploratory nephrotomy.

The extraperitoneal operation should always be done, while if the perinephric and paranephric tissues are markedly involved some surgeons do an extracapsular rather than the more common intracapsular extirpation. Tuberculosis elsewhere is no contra-indication if the process is not too extensive or too active. There is always some danger of the shock, depletion, and other constitutional disturbances incident to a severe operation, lighting up a tuberculous focus elsewhere, but experience shows that this is unusual. Pregnancy is not a contra-indication to this operation if otherwise indicated. If there are other secondary tuberculous lesions, such as in the epididymis, glands, etc., or if the primary foci can be determined they should be removed at the same time if possible. If tuberculosis is advanced elsewhere, nephrotomy or nephrostomy is often a preferable operation, while if after this operation the fever, constitutional symptoms, etc., disappear or markedly abate, a secondary nephrectomy may be done if the ureteral catheter and the functional tests show the other kidney to be healthy.

According to Kelly the ureter, if diseased, and even the portion of the bladder surrounding the ureteral opening, if involved in the tuberculous process, should be removed at the same time as the kidney, or at a later operation if the patient's condition does not warrant it being done primarily; Kümmel inserts a platinum needle into the lumen of the ureter from above and heats it to a white heat, and Bevan cauterizes the ureteral mucous membrane with pure carbolic acid, although some surgeons believe that the ureter had best be let alone, as it usually heals after removal of the kidney. In some cases, however, a persistent sinus is left, while in other cases it is impossible to cure the bladder until a secondary ureterectomy is done.

Involvement of the bladder, even if advanced, is no contra-indication to nephrectomy, and it is striking how frequently improvement takes place after such an operation even in very severe cases; in fact, vesical tuberculosis

secondary to nephrophthisis can rarely if ever be cured without nephrectomy, as the absorption from the diseased kidney and the colicky pain continually tend to lower the patient's general resistance, while the secretions from the diseased organ constantly irritate the mucous membrane. Sometimes after nephrectomy the bladder heals spontaneously, while if tuberculous cystitis persists and, although showing signs of improvement, shows no definite tendency to heal, besides the usual constitutional measures local treatment may be employed, Rovsing finding that instillation of solutions of carbolic acid, 5 to 6 per cent., is the most effective local treatment. In very severe cases opening and draining the bladder and keeping the patient in a bath for some time may be necessary.

As renal tuberculosis is always secondary, and as it is impossible to determine whether all the tuberculous foci have been removed by operation, these patients should be most carefully watched for a considerable period of time subsequent to the operation, and hygienic, dietetic, climatic, and medicinal treatment carried on and possibly also treatment with tuberculin.

Nephrotomy or *nephrostomy* is only justified when the patient's condition is such that a nephrectomy is impossible, when both kidneys are involved, or when ureteral catheterization cannot be performed. After the nephrotomy, if the condition of the patient markedly improves, as is often the case, and if we have been able to determine the functional ability of the other kidney, a secondary nephrectomy is advisable in many cases. In severe bilateral disease marked improvement may follow this operation, which may be performed first on one kidney, then on the other.

There is a great temptation to do a *partial resection* or *partial nephrectomy* if the tuberculous focus seems definitely localized, and Küster, Morris, Israel, Bardenheuer, and others have done this with success; but in the great majority of cases some tuberculous foci are left behind in the parenchyma, and for that reason the great weight of evidence is in favor of absolutely abandoning this operation in favor of total nephrectomy except in those rare cases of bilateral disease where it seems to be more indicated than nephrotomy. Morris has reported 7 cases of partial resection, in 3 of which a secondary nephrectomy was necessary, while the remaining 4 were alive and well from two and one-half to four and one-half years after the operation. Williams had one patient well after four years; Albarran one of double kidney, in which only one side was involved, and this was removed successfully, and Lessander a successful case in a horseshoe kidney.

In the case of perinephric abscess secondary to renal tuberculosis, opening and draining the abscess is all that is done at first, while later secondary nephrectomy may be necessary. After the former operation, as well as after nephrotomy, a persistent fistula is not uncommon. A certain number of cures have been reported by local treatment through the urethra, but in all probability these have been cases of ureteritis where the kidney was affected little if at all.

The results of operative treatment both as regards immediate and ultimate results have been, in the main, favorable, although figures in the latter connection are more difficult to obtain and, as a rule, less definite. The operative mortality, which formerly was from 20 to 25 per cent., is now from 3 to 10 per cent.; Casper found that in the practice of five surgeons before the use of the cystoscope, the ureteral catheter, and the functional tests, the mortality in 139 cases was 21.7 per cent., while after the use of

these methods the mortality in 130 nephrectomies by the same surgeons was 10 per cent; Rovsing, in 112 nephrectomies, has reduced this mortality from 13 to 3.3 per cent. The operative mortality in the earlier and later series shows better than anything else the enormous benefit derived from the modern methods of diagnosis. In 1892 Tuffier reported 25 nephrectomies with 12 deaths and only 2 definite cures; in 1900 Pousson collected 600 cases, with a mortality of 21.3 per cent., while the operative mortality in the newer series is 3.5 per cent. in Albarran's, 3.3 per cent. in Rovsing's, 4.8 per cent. in Wildbolz's, and 7 per cent. in Kelly's. As regards the ultimate results of nephrectomy, the figures are very encouraging. Kümmel reported that 32 of 43 patients were living and well some time after the operation; Albarran was able to follow 39 for a considerable period of time, and only 5 died of further tuberculosis; Kelly got a complete cure in all of 21 patients in whom the bladder was not involved, and in 18 of 36 where it was extensively diseased, the cures being from two to twelve years; Israel in 29 cases got cures of from one to nine years in 11; Küster, 11 complete cures of from one to seven years in 17 cases; Schede, 16 cures of from one to ten years in 22 cases; and Czerny, 11 cures of from one to twenty-one years in 27 cases, in 16 of which secondary nephrectomy was done.

As regards nephrotomy, in a series of 72 cases from different surgical clinics, 7 were cured completely, 18 had a persistent fistula, 28 required a secondary nephrectomy, and 21 died. As regards kidney resection, few figures are obtainable. Morris reports 7 cases with 4 cures of from two to four years, while a few isolated cases of cure have been reported by various surgeons.

Medicinal, Climatic, and Hygienic Treatment: Tuberculin.—Some believe that it is advisable, if an early diagnosis can be made, to first try general treatment, as a cure is theoretically possible and a small number of clinical cures have been reported. It would be most interesting to treat a series of very early cases by climatic, dietetic, and hygienic measures, and this would be comparatively safe if the weight, temperature, general and local condition, and the urinary findings were watched with extreme care, so that at the first sign that the disease was progressing operation could be done at once.

Recently there has been a distinct feeling that specific treatment may prove successful; Birnbaum used tuberculin in the treatment of 23 cases of renal tuberculosis, and found it most helpful, although only in the very early cases in which fever was absent. Marmorek insists on the efficacy of his antituberculous serum, but no series of cases of renal tuberculosis has been treated by this means.

Symptomatic Treatment.—When cure is impossible it is important to make the patient as comfortable as possible by careful attention to both the general and the local symptoms, and such care may be rewarded by considerable temporary improvement. The pain must be relieved in some cases by simple analgesics, in others by opium or morphine; occasionally severe hemorrhage must be controlled; the fever may be reduced by sponging or by antipyretics. In all cases a generous, nutritious dietary, a proper climate and attention to the personal hygiene should be insisted upon if possible. When the bladder is diseased, irrigation, topical application, and hydraulic distention may be employed; while if the pain and tenesmus are intense, it may be necessary to open and drain the bladder; in some cases great temporary relief may be obtained by these means.

CHAPTER XIII.

TUMORS OF THE KIDNEY.

By HUGH HAMPTON YOUNG, M.D.

Hypernephroma.—In the discussion of this subject there is much confusion, owing to the various names that have been used by different authors for the same tumor, viz., perivascular sarcoma, venous endothelioma, lymphatic endothelioma, epithelioma with clear cells, adenoma with clear walls, etc. The descriptions and illustrations which have been given all bear such a striking likeness to the tumor now called hypernephroma that these names should be discarded until a precise nomenclature can be agreed upon.

Etiology.—In a series of 176 cases of hypernephroma collected from the literature by Garceau, the *age* at which the disease occurred is as follows:

Years.	Cases.
1 to 10	4
20 to 30	10
30 to 40	17
40 to 50	48
50 to 60	61
60 to 70	24
70 to 80	3
Not stated	3

The youngest patient was Cheeseman's, a male child, eighteen months old, from whom a tumor weighing four and one-half pounds was removed, and the child recovered. Males are apparently more prone to the disease than females, 71 to 45, according to Keen, and 102 to 71, according to Garceau. All authors are agreed that heredity plays very little part in the etiology of hypernephromata, or in renal tumors in general. Albarran and Imbert found only 5 in 412 cases in which heredity seemed to be a predisposing cause. Study of the cases in the literature reveals very little evidence that trauma or anything else is a real etiological factor.

Pathology.—The first accurate description of the pathology of the tumor was published by Grawitz in 1883, and it was he who first recognized that it arose from aberrant adrenal tissue, which is so frequently found in the kidney. Previous to this the tumor was supposed to be a variety of lipoma. Grawitz called it "struma lipomatodes aberratæ renis," and it was not until 1894 that the name hypernephroma was suggested by Lubarsch. Grawitz made no attempt to classify the growth, saying that at times it resembled adenoma, at others sarcoma, and at others carcinoma; but he gave the following reasons for his belief in its adrenal origin: (1) The position of the growth under the capsule where adrenal "rests" are generally found; (2) the resemblance of its most characteristic cell to those of the adrenal;

(3) the characteristic fatty infiltration of the tumor cells of the adrenal, which is a constant feature of the cortical cells of the adrenal, but is never seen in the normal renal cortex; (4) the presence of a capsule which separates it from the adjacent kidney substance; (5) the arrangement of cells in columns, as in the fascicular portion of the adrenal cortex; (6) the amyloid degeneration in the bloodvessels, which is rarely seen in other tumors, and the fact that the metastases from these renal tumors exactly resemble those of tumors which are definitely of adrenal origin.

Since the publication of Grawitz there has been much discussion and confusion in the literature in regard to the histogenesis of these tumors that we may quote from Garceau's study of the question in his book on *Tumors of the Kidney:*

"A perusal of these views shows immediately how confusing is the whole question of classification of these tumors. The arguments for and against are ingenious and interesting. So far no uniformity of opinion has been reached, and those who are in doubt about the question are in greater numbers than those who have ventured to definitely and positively classify the growth.

"Those who prefer to call the tumor an endothelioma believe in the proliferation of the endothelial cells of the bloodvessels and lymphatics. Among these are Manasse and Driessen. The latter especially is sure that the lymphatics are largely interested in the production of this growth, and he thinks that the tumor is the result of proliferation of the endothelial cells of the lymphatics. Manasse is likewise a strong supporter of this view, but he shows the uncertain state of his mind in regard to them when he subdivides them into three classes: the endothelioma of lymphatics, the endothelioma of veins, and the angiosarcoma.

"Carcinoma is suggested by the alveolar formation, and were this the only typical appearance of the growth, there would be good reason for maintaining this exclusive view in regard to the growth. The epithelial-like cells of which the growth is composed are strong evidence that the growth is of a carcinomatous nature; but the mixed character of the histological structure in the same tumor militates largely against this view. Burkhardt tried to overcome the difficulty by suggesting the names 'malignant adenoma,' 'carcinoma simplex,' and 'medullary carcinoma' for the growth, but this subdivision merely creates more confusion. Those who call the growth adenoma have much to fall back upon. The arrangement of the cells in rows and double rows with an intervening space suggests strongly, on superficial examination, adenoma formation; but the capillary network and the intimate association of the tumor cells with the capillaries is decidedly against this view. Sudeck was the first to insist that adenoma was the correct interpretation, but his views have been, as we have seen, largely discountenanced by the majority of observers. The frequent isolation of the cells, in many cases their grouping in small masses or chains, hardly recalls the typical adenoma.

"Those who hold the view that the tumor is a sarcoma are quite numerous. Manasse, Ulrich, de Paoli, Busse-Beneke, Lubarsch, and Bland-Sutton were all more or less inclined to the belief that the tumor was a sarcoma. Bland-Sutton is not sure that these tumors are of adrenal origin, and without committing himself positively, inclines to the belief of a sarcomatous nature. The strongest proof of sarcoma is the disposition of the cells around the vascular tufts, the angiosarcoma, which is seen in the more typical form

in other parts of the body. De Paoli was sure that he could trace the blood-vessels into the alveoli themselves. The alveolar arrangement is explained by some authors as a type of alveolar sarcoma.

"In discussing tumor classification we must bear in mind the histogenetic and the morphological criteria. The type of cells found in this growth is unquestionably epithelial, and this at first sight would seem to militate against the theory of a sarcomatous nature. But if we examine into the embryology of the adrenal the latest views are to the effect that the adrenal is developed from the mesenchymal cells. This is Minot's view, and no other more satisfactory has been given. Histogenetically, therefore, these adrenal cells are capable of giving rise to a connective-tissue growth, a sarcoma. If we adopt histogenetic criteria alone, then the growth is a sarcoma. Morphologically, however, it resembles an adenoma or a carcinoma. It is obvious that it is impossible to definitely decide in regard to the nature of the growth. It is evident, consequently, that until some definite agreement shall have been decided upon in regard to tumor classification, we cannot do better than to relegate these growths to a class by themselves. The fact that they develop from adrenal 'rests' in the kidney is now so commonly admitted that there are few who deny this. It seems to be an incontrovertible fact. The best name for the growth, therefore, one which suggests their pathogenesis, is that first proposed by Lubarsch, hypernephroma."

Croftan found that hypernephromatous tissue had the same properties in starch solution as an extract obtained from the adrenal gland, and proposed this as a differential test.

The occurrence of adrenal rests has been the subject of considerable study. Imbert found them in different organs in 92 out of 100 autopsies, in the kidney in 8 per cent. of the cases. They are usually found in the upper pole beneath the capsule, and this is the usual site for hypernephromata. In some cases they are within the medullary portions of the kidney. Hypernephromata have been reported as primary tumors in other organs. In 163 cases Keen found 157 in the kidney, 3 in the adrenal, 2 in the liver, and 1 in the uterus. The writer has seen a case in which a leg was amputated for sarcoma of the tibia, the microscopic study of which showed a hypernephroma, although there was no sign or symptom of a tumor in the region of the kidney. The location of hypernephromata in the kidney is usually in the upper pole, just beneath the capsule. There may be one nodule or several, which may be small or large, the whole tumor varying in size from that of a pea to that of an adult human head. They are usually encapsulated and sharply contrasted with the surrounding or adjacent renal tissue, which often shows evidence of atrophy and interstitial nephritis.

The consistence in the smaller tumors is often firm, but when the tumor is large it is usually soft, and blood cysts are often seen. Areas of more or less extensive hemorrhage in the tumor tissue are found on section, and large areas of necrosis are common.

Histology.—The similarity to adrenal tissue is most marked in the small hypernephromata. The stroma is largely composed of capillaries upon which the cells lie without intervening tissue, ranged in rows, sometimes two or three deep. These cells are, as a rule, rather larger than the normal adrenal cell, polygonal in shape, and contain much fat. Giant cells and karyokinetic figures are sometimes seen. Chemical examination reveals glycogen and lecithin, which along with fat are also found in normal adrenal

cells. In the large tumors there is a certain amount of fibrous tissue in the capillary stroma, and the polygonal cells are often arranged in distinct alveoli. This alveolar arrangement has given rise to the opinion that the disease is a carcinoma or an alveolar sarcoma. Papillary formations are also seen, and the arrangement in rows is composed of more cells than in the small tumors. In a study of 36 mounted specimens, Garceau found the alveolar type in 22, and the papillary, mixed with the alveolar, in 4 cases. Blood spaces, some dilated vessels, others hemorrhagic in character and at times forming cysts of varying size, are seen. In the larger tumors necrosis not infrequently occurs, generally in the centre of the mass and most remote from the peripheral blood supply.

Invasion.—As remarked above, the tumor may be only a small nodule in an otherwise healthy kidney. With time, however, the tumor invades the kidney more and more, causing first a pressure atrophy, finally in some cases completely replacing the kidney and forming a large lobulated irregular mass, which is usually completely encapsulated. In the malignant cases neighboring structures may be invaded, but this is rare, as is also invasion by the lymphatics. As a rule, the systemic invasion is through the veins. It is not uncommon to find the renal veins invaded by the tumor, which may conform to the shape of the vessels and grow intravenously to great distances. In one of the writer's cases the vena cava was filled with a non-adherent growth, which extended upward through the diaphragm and down to the brim of the pelvis. The renal vein on the opposite side was invaded almost up to the kidney. Another case is reported in which the thrombus extended into the auricle of the heart. Loosened emboli are carried through the blood current to remote portions of the body. Metastases have been found in the brain, bronchi, diaphragm, heart, liver, intestines, omentum, pancreas, pleura, peritoneum, skin, uterus, urethra, and in various portions of the bony skeleton. These metastases reproduce exactly the histological characteristics of the parent tumor, and the fact that they are not transmitted by the lymphatics and never invade the urinary tract below the kidney are very strong arguments against their being considered carcinomatous. In rare cases the tumor mass grows out into the renal pelvis, but no case has been found in which the ureter was invaded.

Symptoms.—Hypernephromata are so variable in their growth that the symptomatology is by no means uniform. Many of the cases in which the tumor is small, benign in its character, and very slow of growth, may present no symptoms, and in such cases the tumor is often discovered postmortem. In others a small tumor may be accompanied by abundant symptoms, and if at the lower pole of the kidney, may be detected by palpation. In those cases in which the tumor assumes a malignant character the growth may be rapid and the symptoms marked. The three cardinal symptoms are hæmaturia, pain, and tumor.

Hæmaturia.—This is the most frequent sign of malignant tumors of the kidney in adults. In 83 cases reported by Desnos, hæmaturia appeared before every other symptom in 41 cases; Israël places it at 70 per cent.; Denoclara at 65 per cent.; Albarran at 54 per cent., and Küster at 52 per cent. Garceau found hæmaturia a prominent symptom in 50 per cent. of 106 cases, but in 35 cases it was absent. In some cases it is the sole symptom, and in one of Israel's cases had been present for twelve years.

Generally, the bleeding comes on insidiously and continues several days,

after which it may not reappear for several months. The attacks become more frequent, as a rule, with the progress of the growth, and often recur with regular periodicity. The urine is usually markedly colored with blood, and frequently large clots are passed. Rarely the advent of bleeding is presaged by a dull pain in the side, sometimes simulating renal colic. In such cases the ureter has usually become blocked by a clot, and for a time the urine voided may be free from blood. This is usually followed by cessation of the pain, accompanied by the sudden re-appearance of blood and the passage of clots.

Garceau thinks that the hæmaturia which occurs in the early stages is due to congestion, that later the blood may pass directly into the urinary tubules in places where the neoplastic capsule may be wanting, and finally when erosion into the pelvis occurs, abundant hemorrhage may come from this. Desnos says that it is sometimes the renal parenchyma and not the tumor which bleeds. Statistics show that the hemorrhage is not influenced by position or occupation, occurring as frequently at night as during the day. In spite of their frequent repetition, these hæmaturias rarely weaken the patient so greatly that operative intervention is necessary to stop the bleeding. The sudden change from very bloody to perfectly clear urine is of considerable diagnostic importance, showing that the ureter has become blocked.

Worm-like blood casts of the ureter are not uncommon.

Pain.—This is often absent for a long period, and is very variable in its character. Many hypernephromata reach considerable size without causing any pain. In some it is merely a dull ache in the lumbar region, but occasionally the pain runs downward along the sacral and pelvic nerves. It usually comes on spontaneously without relation to exercise or bodily position, and in some cases may be quite severe for a short while. When the ureter becomes blocked by a clot severe colicky pains exactly simulating the passage of a calculus—radiating to the groin and scrotum—usually come on. Pressure on the kidney does not usually increase the pain, but the patient is sometimes unable to lie on the affected side.

Tumor.—When the growth is of the voluminous type a perceptible or palpable tumor of the flank is one of the most important symptoms. According to Garceau, tumor is usually the first sign of hypernephroma, and in 143 cases it was present in all but 17 cases. In many of the cases, in which the disease begins at the upper pole of the kidney, palpation will not detect it until late, and in a few cases in which the tumor remains small it is never discovered during life. The growth generally preserves the usual shape of the kidney, and may be uniformly smooth. Very often it is irregular, lobulated, or nodular. When the tumor is large the flank is deformed and the shape of the tumor may be apparent on inspection. In cases of moderate size it may be perceptible only on bimanual examination. The usual site of the tumor is in the lumbar region, but extending forward in the abdominal cavity, and generally lying between the ribs and iliac crest, with no space between the tumor and the lumbar muscles. Small tumors are often movable, but the larger ones are generally fixed.

In consistence these tumors are usually firm, at times hard and nodular. Sometimes fluctuation can be made out in cystic or necrotic portions of the growth. Percussion gives a sonorous sound in front of the mass, even in the large tumors, and lumbar percussion shows dulness which extends to the

vertebral column. The *x*-ray has not as yet proven reliable in demonstrating tumors of the kidney.

In determining the character of the tumor its relation to the colon is of great help, and the following is quoted from Garceau: "The kidney is normally situated behind the colon, and when enlarged by a tumor it must develop in the layers of the ascending or the descending colon; hence the colon will be found in front of the tumor or toward its inner side. Tumors of the liver crowd the colon down, and may override it; tumors of the stomach also crowd the colon down; while tumors of the pancreas almost invariably appear above the transverse colon, and in a few instances behind it. A tumor growing in a movable kidney may enter the central zone, but unless fixed it can be slipped back into position. Tumors of the adrenal push the colon forward and inward. The central region, besides uterine and ovarian tumors, may contain growths of the small gut, the mesentery, omentum, and also enlarged retroperitoneal glands. The spleen must be on the outside of the descending colon, but if greatly enlarged may override it entirely; there is no line of resonance between the kidney dulness and the vertebral spines, as there nearly always is in the case of splenic enlargement. Tumors ordinarily close to the abdominal wall may in consequence of adhesions be separated from it by intestines; in this case there will be tympany in front of them. Tumors of the spleen, liver, and uterus may present these characteristics, and especially tumors of the ovary."

Changes in the Urine.—The amount and character of the urine remain normal, as a rule, until late in the disease. A small amount of albumin may be present in the bloodless intervals, and may be due to nephritis or pyelonephritis. The presence of casts is rare, and very few cases have been reported in which bits of tumor tissue were found in the urine. Even with very marked involvement of a kidney by a neoplasm it is often remarkable how valuable, functionally, it remains. In some cases, however, no urine is obtained from the affected side. As remarked above, the hemorrhage is very variable as to amount and frequency of occurrence. In certain early cases it may be hardly sufficient to color the urine. It is more common, however, to have a very evident hemorrhage which lasts a few days, and is followed by a more or less prolonged period of normal urine. Glycosuria has been noted in a few cases.

Other Symptoms.—Renal neoplasm may produce symptoms due to compression of surrounding structures. One of the most common is varicocele, and it is considered quite significant when present on the right side. In 20 cases Kapsammer found marked circulatory disturbances of the inferior membranes and of the abdominal wall. In one of the writer's cases in which the vena cava was almost completely obstructed by a large intravenous growth, the peritoneal veins were greatly dilated, and with the portal veins, which were also dilated, took care of the return circulation from the inferior extremities and the abdomen. Œdema and ascites are sometimes present in such cases. Jaundice may occur, due to obstruction of the common bile duct or extension of the disease to the liver. Only rarely does the tumor growth cause painful symptoms from compression of the nerves, and marked pain in the spine often indicates metastases. Gastric symptoms, nausea, vomiting, and occasionally hæmatemesis have been reported, and may indicate either metastases or uræmia. Dyspnœa may be present.

Cystoscopy.—The advent of the cystoscope has done more to clear up the diagnosis in obscure cases than anything else. By means of the simple cystoscope sufficient data can usually be obtained so that ureter catheterization may be dispensed with. If hæmaturia is present, a red jet of urine can usually be seen to escape intermittently from the affected side. If the urine is only faintly colored, it may be impossible to detect any difference between the two sides; and if the hemorrhage is very great, it may be difficult to get a field clear enough for accurate observation. For the latter cases the "evacuation" cystoscope, which permits of rapid cleansing of the bladder, may be very helpful. In some cases the ureteral orifice may be abnormal—it may be dilated, as a result of the pressure of clots, or it may be surrounded by hyperæmic, swollen, or œdematous mucous membrane. In some cases the simple cystoscope shows nothing definite (especially between attacks of hæmaturia), and ureter catheterization may be advisable in order to determine the functional value of the two kidneys. A small amount of blood from either ureter is of no importance, as it may be traumatic. In determining the renal function, the phloridzin, the methylene-blue, and possibly the freezing-point tests may be made. Radiographs taken after the renal pelvis has been injected with 2 per cent. collargolum may be very helpful by demonstrating the absence of a dilated pelvis or renal cortex, and by showing the relation of the tumor mass to the renal pelvis. The *x*-ray has been disappointing in not showing pictures of renal tumors, but in a few cases indurated lobules have been demonstrated by the plate.

The more simple urinary tests may sometimes be very helpful: If the urine is voided in three separate specimen glasses all three urines will be equally bloody, whereas in vesical and prostatic hemorrhage the last specimen generally contains the most blood, and in some cases the only blood (terminal hæmaturia). The presence of clots in the form of long ureteral casts is diagnostic of hemorrhage occurring above the bladder, but cystoscopy is a much more positive method.

Duration.—In a list of 27 operated cases collected by Garceau the tumor had been present for fifteen years in 1 case, twelve years in 1, ten years in 2, eight years in 2, seven years in 2, six years in 5, five years in 6, four years in 2, three years in 5 cases; but in another list of 89 cases, the duration of the symptoms when nephrectomy was performed was not over a few months in 53 cases. The duration of the disease is generally shortened by the early appearance of metastases, which may be of large size, very painful, and lead to exhausting symptoms, which completely overshadow the renal affection.

In a series of 21 cases collected by Garceau, in which metastases were present and no kidney operation performed, it is a notable fact that in only 4 cases had the duration been more than one year when death resulted. In nearly all of these cases the metastases, particularly of the bones and lungs, were of more moment than the renal tumor.

Diagnosis.—In most cases the patient has not suffered from pain, and the presence of hæmaturia has alone attracted the attention.

The diseases most commonly confounded with hypernephroma are tuberculosis, calculus, hydronephrosis, pyonephrosis, and tumors elsewhere in the abdomen.

Tuberculosis of the kidney is first to be considered and excluded in all cases. In tuberculosis pus is generally present in the urine between the

crisis of hæmaturia, and by careful search tubercle bacilli can generally be discovered. Great care must be taken to exclude the smegma bacillus. The smegma bacillus may be found in the anterior urethra, but never back of the external sphincter, and if the penis is thoroughly cleansed and the anterior urethra irrigated, none of these organisms will be found in the urine voided. As an additional precaution, it is well to have the patient void in three sterile glasses and to make the bacteriological examination from the third glass. If bacteria resembling the tubercle bacillus in form and not decolorizing with acid are found, one can be sure that it is the tubercle bacillus, and the inoculation of animals and the tuberculin test are not necessary. When the results are negative, the latter test may be advisable.

The presence of foci of tuberculosis in other organs may be of great assistance; this is particularly true of the genito-urinary tract, as nodules in the prostate and seminal vesicles or in the epididymis are not infrequently found. Non-tuberculous renal infections are, however, not infrequently associated with prostatitis characterized by more or less extensive induration, often closely resembling tuberculosis of the prostate. The cystoscopic picture of the ureteral orifice is generally of great diagnostic worth. In tuberculosis it is apt to be dilated, often gaping, sometimes ulcerated, and surrounded by an area of vesical tuberculosis; whereas in hypernephroma only a slight hyperæmia or dilatation of the ureteral orifice is seen. Tuberculosis is rarely associated with the great enlargement of the kidney often seen in hypernephroma, but in early cases the diagnosis may be extremely difficult. Ureter catheterization is often necessary.

Renal calculus may also closely simulate hypernephroma. It is usually more painful and the kidney less enlarged, but the writer has seen a case in which the kidney was immense and contained fourteen large stones (several larger than hen's eggs), in which there had never been pain, hemorrhage, or discomfort, and the patient sought relief because of occasional febrile attacks. Bodily movements, especially walking, riding in a rough vehicle, or lifting, usually aggravate the symptoms in stone, whereas they have little or no influence in hypernephroma. The attacks of renal colic are usually more characteristic with calculus, and the passage of a calculus is of diagnostic value; but it must be remembered that blood forms an excellent nucleus for a calculus, and that nephrolithiasis occasionally accompanies hypernephroma. The radiograph is here of great diagnostic value, as it is now possible to demonstrate with it calculi of very small size. Pyuria is not of great diagnostic value, as it may be present both in renal calculus and hypernephroma, although more common in the former.

Hydronephrosis, pyonephrosis, and *perinephritis* may all be associated with an enlarged indurated mass closely simulating neoplasm, and the occasional presence of hæmaturia may make the resemblance close. On the other hand, intermittent distention of the renal pelvis accompanied by tumor formation and crises of pain, which are so characteristic in certain forms of hydronephrosis, the writer has seen in a case of hypernephroma. In this case during the periods of bleeding the tumor mass would occasionally become greatly enlarged. This was always associated with sudden cessation of the hæmaturia (evidently due to blocking of the ureter with a clot) and severe pain.

When hæmaturia is the only symptom it is often very difficult to make a diagnosis, and we must consider not only tuberculosis and calculus (both

of which may present this symptom alone), but also the *essential renal hæmaturia* of Senator and Klemperer, the hæmophilic hæmaturia of Senator, the hæmaturia of pregnancy (Guyon), and the hæmaturia which accompanies certain cases of chronic nephritis (Pousson).

These hæmaturias present a most perplexing and little understood class of renal disorders, and have led to much confusion. It has been definitely shown that hemorrhage may occur from a kidney in which it is impossible to discover any macroscopic or microscopic lesion, and may re-appear with such frequency and abundance as to be serious. Some have asserted that this is almost always associated with a localized nephritis which is sometimes unilateral, but that such is not generally the case has been abundantly proven. The question of such nephritis is, however, of sufficient importance to warrant the catheterization of the ureters in all such cases, both during and between the attacks of hæmaturia. The writer has published[1] a method of diagnostic and therapeutic value in these cases of painless hæmaturia, which consists in the injection of about 15 cc. of a 1 to 3000 solution of adrenalin chloride into the renal pelvis through a ureter catheter. In three cases of essential renal hæmaturia this treatment was followed by a disappearance of the hæmaturia, which at this writing, many months later, seems to be permanent. While it might be possible to completely stop the hemorrhage from a hypernephroma, it seems very probable that it would soon recur and the presence of pain and tumor would of course lead to suspicion of neoplasm.

Other tumors of the abdomen have of course to be considered in making the diagnosis, but we have not the space to do more than call attention to the usual absence of urinary symptoms in such cases and to the general principles of abdominal examination and diagnosis.

The diagnosis of hypernephroma from *other forms of renal tumor* is often impossible.

Carcinoma of the cortex or of the pelvis of the kidney does not usually reach such great size, and the hemorrhage is apt to be more frequent and abundant than in hypernephroma. Pain is generally much more severe, and the disease more rapidly fatal. Pieces of neoplastic tissue are more often found in the urine than in hypernephroma, and occasionally the growth extends down to the ureter and the bladder, where it is visible with the cystoscope; whereas hypernephroma has never been known to spread by the urinary passages, and, as shown before, glandular metastases are rarer than with carcinomata.

Sarcoma of the kidney is essentially a disease of childhood, generally growing rapidly to great size without hæmaturia or pain. It is seen, however, in adult life, and may closely simulate hypernephroma in rapidity of growth, size, and occasionally freedom from pain and tumor. The fact that many of the hypernephromata have been described as sarcomata will be discussed later.

Adenoma of the malignant type is rare and closely simulates adenocarcinoma. Cases of long duration have been reported, but the supposition is that the disease was benign for a protracted period in such cases.

The benign tumors *fibromata, adenomata, lipomata*, etc., are rarely associated with hæmaturia or pain. *Polycystic disease* of the kidney is more apt to be bilateral and free from hæmaturia. In later stages it is accom-

[1] *Journal of the American Medical Association*, 1908.

panied by symptoms of renal insufficiency, headache, nausea, etc., which do not often occur in hypernephroma.

Teratomata and *rhabdomyomata* occur so rarely as to make diagnosis almost impossible. In hydatid diseases of the kidney hooklets may be found in the urine.

Treatment.—Medical treatment, except of a symptomatic or palliative character, is of little use. An early operation should be performed in all cases when the condition of the patient admits of it, and in recognition of this fact an early diagnosis should be aimed at.

Hæmaturia, although slight and painless, should lead to a thorough investigation by exhaustive methods. We have all seen too many cases in which the bleeding was said to be due to malaria, especially in patients from the Southern States. In other cases the hæmaturia has been attributed to renal congestion, varices, essential hæmaturia, renal epistaxis, etc., and on account of the infrequency and benignity of the hemorrhages, cases have been allowed to run on much too long. When a hæmaturia occurs a most careful abdominal examination and microscopic and bacteriological study of the urine should be made, and if these are negative, the radiograph, cystoscope, and ureter catheter should be employed. If the blood comes from the ureter, and tuberculosis, stone, parasitic diseases, etc., have been excluded, the diagnosis will probably lie between tumor and essential hæmaturia (in the absence of evident tumor and pain). Although time is precious in case there should be a neoplasm, it would seem advisable at first to try to bring about a cessation of the hemorrhage by rest and internal medication (calcium lactate, etc.), or, these failing, by the injection of adrenalin into the renal pelvis through a ureter catheter.

If the bleeding is stopped by these methods, the physician should be aware that he is taking a certain amount of risk, that he may have caused a cessation of hemorrhage from a renal tumor (because we know that the intervals between bleedings may be very protracted, even months or years), and make frequent abdominal examinations in search for the appearance of a tumor, and study the urine for microscopic hæmaturia.

When medical measures fail to stop the hæmaturia, or when a palpable tumor is present, operative intervention is indicated and should not be delayed. When the tumor is large, operation should usually be undertaken unless complications of considerable severity, sufficient to cause the patient to be denied a chance of cure or relief, are present; for it is true that in some cases the pain is so considerable that operative relief should be afforded, even though the chance of cure is remote.

Operation.—Before this is attempted the patient should be in the best possible condition. If greatly weakened by hemorrhage, it may be possible by rest in bed, internal medication, water in abundance, salt solution by rectum, infusion, or transfusion to stop the bleeding. A careful study of the renal function should be made, the daily output in amount, specific gravity, urea, and total solids being of particular value. The freezing point of the blood is also valuable, as showing renal efficiency, and, when the patient is strong enough, ureter catheterization to determine the comparative value of the kidneys—and particularly the probable ability of the supposedly sound kidney to assume the work of both—should be attempted. If the hemorrhage continues and immediate operation is not to be thought of, the injection of adrenalin through a ureter catheter may be employed.

Operative technique is hardly within the scope of this article, but it may be well to state that complete nephrectomy should almost always be done, and that it may be performed either intra- or extraperitoneally. Nearly all authors are agreed that the lumbar extraperitoneal route is preferable for all but the large hypernephromata. By extending the oblique lumbar incision downward and inward it is possible to get a very large field of operation, to see the depths of the wound, and to ligate the vessels of the pedicle separately (after carefully examining them to see that no intravascular neoplastic growths are present). It is agreed that the fatty capsule, the adrenal and adjacent glands should be removed with the kidney if possible, but that it is unnecessary, in the case of hypernephromata, to remove much of the ureter.

The intraperitoneal route is in favor with most surgeons for large tumors, especially those in children, and with some for the smaller tumors. The advantages claimed for it are the large field obtained, the ability to palpate the other kidney, to ligate the bloodvessels of the pedicle before attempting to free the kidney from the surrounding adhesions which are apt to bleed profusely, to remove the fatty capsule, glands, and adrenal more thoroughly, and to detect thrombotic growths in the renal vein or vena cava before attempting fruitless procedures on the kidney.

Operative Results.—In a compilation of the results after nephrectomy for malignant tumors, Desnos says that before 1891 the mortality was great; Guillet placed it at 66 per cent., Siegrist at 52 per cent., and Chevallier at 58 per cent. From 1890 to 1895 Wagner's statistics were 25 per cent., Küster's 24 per cent., and Rovsing's 20 per cent. In 1898 Heresco collected 165 cases, with an operative mortality of 19.5 per cent. Of these 52 were infants with a mortality of 17 per cent. The results were known in 24 of the 53 infants operated upon; 16 of these died later and 8 had no recurrence for periods varying from nine months to six years and a half. Of the 112 adults operated upon, 89 survived, of whom 62 were followed; of these 36 were alive after an interval varying from two months to seven years. Forgue found that 28 patients in whom nephrectomy had been done for malignant tumor were alive four years or more after the operation.

The statistics of operative results in hypernephroma itself are unfortunately meagre. Garceau states that in 176 cases of hypernephromata collected by him there were 143 nephrectomies, with 33 operative deaths (occurring within two months after the operation), a mortality of 23 per cent. These statistics cover a period of fifteen years, and the mortality is probably much better now. Israel has published 17 cases of nephrectomy for hypernephroma. Of these, 16 were operated upon by the lumbo-abdominal extraperitoneal route, with 3 immediate operative deaths from heart failure or shock. In 4 cases death from recurrence or metastases resulted in five months, eighteen months, and two years (2 cases) respectively. In all of these cases the patient was greatly benefited, although all were extensive. Eight patients were still alive and well when the publication was made. In 3 cases the operation had recently been performed, but the patients had left the hospital apparently well. In 2 cases two years, in 2 cases six years, and in 1 case nine years had elapsed since the operation. When it is considered how long the tumor had generally been present, its size and the weakened condition of many of these patients, the results are very encouraging. With early diagnosis and prompt operation the mortality should be reduced greatly.

Carcinoma of the Kidney.—As a result of a more careful pathological study of kidney tumors, carcinoma has become in recent years exceedingly rare. The great histological variations in hypernephroma, the transition in various parts of the tumor to the adenomatous, carcinomatous, or sarcomatous type, often render the true nature of the tumor extremely difficult to determine. Undoubted carcinoma of the kidney is exceptionally rare, and its existence is doubted by some authors. Neuhauser[1] in a study of 69 tumors from Israel's clinic found that 65 were apparently typical hypernephromata; 2 of the tumors he classed as hypernephroid carcinomata and 2 as hypernephroid sarcomata. In the 2 cases designated as hypernephroid carcinoma, portions of the tumors were typically cancerous and formed cell nests not unlike those seen in mammary cancer. Other portions had the typical appearance of true hypernephroma. He is very positive in his statement that all carcinomata of the kidney arise from hypernephroma. Albrecht[2] in a report of two tumors from the service of Hochenegg, occurring during a period of ten years, found 28 which were malignant hypernephromata; 3 were true sarcomata and 1 was a squamous-cell sarcoma arising from the pelvis of the kidney. He considers an adenocarcinoma arising from the kidney parenchyma a tumor of the greatest rarity. One did not occur in his series of 32 cases, and he does not state that he has ever seen one. On the other hand, however, Garceau has reported three carcinomata, about the nature of which there is apparently no doubt, while we have been able to find one true adenocarcinoma in the material in the Johns Hopkins Hospital. This has been reported by Cullen.[3] Morris is of the opinion that primary renal carcinoma is a rather common occurrence. Adami is of the opinion that carcinoma arising from the kidney parenchyma is more common than generally admitted, and considers that many of the tumors which bear a close relationship to the hypernephroma have really their primary origin in renal tissue. He considers that two organs so closely related embryogenetically as the renal cortex and the adrenal may easily produce tumors which possess closely related characters. Of the 4 cases which we have been able to verify, 2 were in women and 2 in men, and the ages of the patients ranged from twenty-six to forty years.

Pathology.—According to Waldeyer,[4] carcinoma of the kidney arises from a proliferation of the renal tubules. The infiltrating form is agreed, almost by common consent, to be the most frequent form of carcinoma, and of the 4 cases referred to above, 3 were of the infiltrating type, 1 only being a definite adenocarcinoma. "The most characteristic feature of the infiltrating form is the grouping of the cancer cells in irregular masses without any definite arrangement. The cells infiltrate the tissues, crowding into them and growing in among the normal cells. The interstitial tissue, the tubules, and the glomeruli are less invaded. In parts also the cancer cells are arranged in columns and cords of regularly disposed columnar epithelium, presenting on section a striking resemblance to the tubular arrangement of the normal kidney. In other places the cells are arranged in masses without any definite form, and they enter into the surrounding

[1] *Archiv f. klin. Chir.*, 1906, vol. lxxix.
[2] *Ibid.*, 1905, vol. lxxvii.
[3] *Journal of the American Medical Association*, 1905.
[4] *Virchow's Archiv*, 1867, Band xli, 493.

renal tissue. Another distinctive feature of carcinoma is the arrangement of the cells in alveoli, large and small, which are surrounded by stroma of connective tissue, the cells being arranged close together one against another."

In none of the infiltrating forms was the kidney markedly increased in size; the shape of the kidney is usually well preserved and the cancerous growth invades it quite regularly, producing a uniform enlargement. On section the carcinomatous areas are grayish white or yellowish, and hemorrhagic areas are quite common. The growth shows a greater tendency to break through the capsule and invade the surrounding structure than does the hypernephroma. The tumor grows into the bloodvessels, especially the veins, and the pelvis is invaded in a manner similar to hypernephroma. The lymph glands of the pelvis show early metastases, and the liver, lungs, and other organs are invaded early through the medium of the bloodvessels.

In the case of adenocarcinoma the tumor mass was somewhat kidney-shaped, irregular in outline, and about five times the size of the normal kidney. On palpation the tumor seemed to be cystic. On section no renal tissue was demonstrable, the greater part of the tumor being soft, and consisting of a spongy homogeneous tissue resembling carcinoma. The capsule was composed of a dense fibrous tissue. On microscopic section the tumor was seen to be a glandular growth; the gland type was particularly well-marked, and the acini were very regular in size. The epithelial cells were low, cuboidal, or cylindrical in type. The nuclei stained darkly and were round or oval. There was a very small amount of stroma present. The cells of this growth had a striking resemblance to those of the collecting tubules of the kidney. There was no invasion of the ureter or bloodvessels by the growth, as is seen in infiltrating forms. The metastases to the liver, lungs, and retroperitoneal glands preserved the adenomatous forms peculiar to the tumor.

Symptoms.—The first symptom noted in the infiltrating forms was acute agonizing pain in the region of the affected kidney, of a radiating character in one case. In the case of adenocarcinoma, a tumor mass was the first symptom. Hæmaturia was persistent and abundant in one case, slight and recurrent in two, and absent in one. A tumor mass was noted in three cases; in one case no enlargement of the kidney was demonstrable. The duration of symptoms varied from one to four months, and death occurred in the three infiltrating forms in from seven weeks to seven months after the onset of the first symptoms. In the case of adenocarcinoma the patient died six years after operation with extensive general metastases.

Diagnosis.—It is impossible to clinically differentiate carcinoma from malignant hypernephroma or other malignant forms of kidney tumor. With the exception of the early, severe, radiating pain, there is no differential point which would make one suspect the possible cancerous character of the disease.

Treatment.—(See section on Hypernephroma.)

Malignant Papillary Cyst Adenoma.—A separate classification is usually reserved for this rather uncommon tumor. It bears a close resemblance, histologically, to benign adenoma, and most frequently a papillary type of tumor prevails. While, histologically, the picture resembles closely benign adenoma, at times a distinctly malignant picture is seen. These tumors are almost always malignant, and should be treated as such. The kidney is seldom much enlarged, is nodular and hard, and, on section, shows numerous small cystic areas full of a gray or deep red

material. At times the growth becomes infiltrating, and in such cases gives the histological appearance of the infiltrating type of carcinoma. The *symptoms* and *treatment* are identical with those described under Hypernephroma.

Adenomata.—These may be either benign or malignant, isolated or multiple. The small multiple adenomata of the kidney are not infrequently found at autopsy, and vary in size from a millet-seed to that of a pea. As a rule, they are associated with some form of nephritis, and produce no symptoms in themselves; they are discovered, as a rule, postmortem. They are usually found beneath the capsule, but occasionally are seen within the parenchyma of the kidney. The large variety is much more rare, is usually seen in adults after the age of forty years, and forms a spherical, encapsulated mass, which rarely reaches the size of a small orange. On section, these tumors are grayish white in color, friable, frequently infiltrated with blood, and sometimes studded with cysts. According to Garceau, there is a tubular form resembling adenoma of the liver, characterized by cylindrical cells, with a light, connective-tissue stroma. Alveolar and papillary forms have also been described. Benign adenomata usually present no symptoms, even the large forms rarely producing any discomfort, hæmaturia or palpable tumor.

The so-called malignant form of adenoma resembles carcinoma of the kidney so closely that it seems unwise here to attempt to differentiate them. In some cases it has the histological structures seen in benign adenoma, but destructive invasion of surrounding tissues, the gradual involvement of much of the kidney, and the absence of capsule show its malignant character. The symptomatology, progress, and prognosis is similar to that of carcinoma, and diagnosis is usually made only at operation or at autopsy. Early nephrectomy is here also the rule.

Sarcoma of the Kidney.—Many cases of sarcoma of the kidney have been described in children, but careful microscopic examinations have shown that they were almost always mixed tumors, which will be described in another portion of this chapter. Sarcoma of the kidney is much rarer than hypernephroma in the adult. In Rosenstein's 30 cases there were only 8 in which the patient was over twenty years of age, 6 being in the period from forty to sixty years of age. In the adult these tumors do not reach the enormous size seen in children, and Albarran remarks that they seldom are larger than two fists in size. He recognizes three forms: (1) Those which start in the capsule and which may for a time be encapsulated and more or less separated from the kidney; (2) those in which the tumor has its origin in the region of the hilus; and (3) those beginning in the parenchyma, which are the most frequent, and are present either in an infiltrating or a nodular form. In a case of spindle-cell sarcoma of the kidney in a woman, forty-nine years of age, reported by Garceau, which had been present for three years, the kidney and tumor measured 16 x 10 cm., and on section it was seen to be a new-growth of globular outline, about 10 cm. in diameter, of grayish color, homogeneous, somewhat transparent around the edges, and more opaque and yellowish and necrotic in the centre. Reaching out into the normal renal tissue were several small nodules, and a mass of the tumor was seen projecting into the renal vein, which was greatly enlarged. The upper end of the kidney was normal, and its substance was grooved at its point of contact with the tumor, which was beneath it. The microscope showed that it was entirely made up of spindle cells.

We have had the opportunity of studying two cases of pure sarcoma of the kidney occurring in children: one was a small, round-cell sarcoma occurring in a girl, eighteen months of age, and noticed eight weeks before death occurred; the other in a boy, four years of age, of a pure, spindle-cell variety, had been noticed three months before death occurred. Both tumors were extremely large, filling the whole abdomen on the side of the tumor; the capsule was dense and thick, and closely adherent to surrounding structures; the ureters were not involved, but the growth had extended into the renal bloodvessels. The kidney was entirely replaced by tumor mass in each case. In the spindle-cell sarcoma several cysts were present, and it had not degenerated. The round-cell sarcoma, however, was very soft, the entire internal portion of the tumor having broken down. Histological examination from different parts of the tumor failed to reveal any of the elements commonly found in mixed tumor. In the round-cell sarcoma large islands of closely packed cells, separated by rather a dense, fibrous stroma, were the prevailing feature. In the spindle-cell sarcoma no fibrous stroma could be observed, the sections simply showing closely set large spindle cells. In the case of the round-cell sarcoma, metastases were found in the lungs and liver, and in the spindle-cell sarcoma the retroperitoneal lymph glands were involved.

According to Garceau, the capsule is most frequently the origin of the growth, from which place the soft tissues are invaded. The tumors, as a rule, are soft and homogeneous on section. They are most frequently nodular, but may be diffuse. On microscopic examination both the small and large round-cell and the spindle-cell variety of sarcoma have been found in different cases. In some cases there is considerable fibrous tissue, enough to designate the tumor as a fibrosarcoma. An angiosarcoma of the kidney has been described, but the microscopic appearance was evidently very similar to that which is recognized as hypernephroma, and it seems best at the present time to classify these tumors as identical. Sarcoma of the kidney is very similar to that of malignant hypernephroma of the kidney in its progress, symptomatology, and prognosis. The tumor, as a rule, remains encapsulated and metastasis occurs through the veins. Occasionally the lymphatic glands are involved, and sometimes the surrounding structures are invaded. The extensive intravenous, neoplastic thrombi, which are so frequently seen in hypernephroma, are also seen in sarcoma. In some cases the duration of the disease is only a few months, but in other cases (particularly the spindle-cell variety) it may be several years.

Symptoms.—The three cardinal symptoms of renal tumors, hæmaturia, pain, and tumor, are found in cases of sarcoma, and it is almost impossible to make a differential diagnosis between hypernephroma and sarcoma. Very large tumors of slow growth and long duration are generally hypernephromata, but in some cases the hypernephroma may be as rapidly fatal as sarcoma without the tumor reaching the enormous size that is usually seen. The methods of examination which has been described at length in the examination for hypernephroma apply in cases of sarcoma, and they need not be repeated here. The treatment should consist in early nephrectomy in all cases; the prognosis even then is not good, owing to the frequency of metastases.

Embryonic Tumors of the Kidney.—As in the case of other organs, the kidney is subject to tumors arising from inclusions or occlusions of

apparently embryonic tissue; these, however, differ somewhat from the fetal tumors of other organs. The typical dermoid cyst of the kidney is very rare indeed, only two cases having been reported: one by Haeckel[1] and one by Paget.[2] Pure rhabdomyoma of the kidney is also extremely rare. The typical mixed tumor of the kidney is, however, not a very rare occurrence in children. The histogenesis of the tumor is rather indefinite, Weigert[3] claiming that they arise from the Wolffian body, and Wagner[4] that they arise from the early kidney segment or "urniere." Muus[5] describes six tumors to which he has had access, and discusses the origin of these growths. He believes that they occur as a result of some very early pathological process in the embryonic kidney, a certain portion of early developing kidney being thus retarded in growth; the rest of the structure develops along normal lines.

These tumors were early recognized, and seemed to have caused much confusion, being designated variously as "embryonic adenomyosarcoma," "embryonic adenoma," "sarcoma carcinomatosum," "adenosarcoma," etc. They occur for the most part in young children, one case having been reported, however, in a woman thirty-four years of age. The age of the majority of the patients range from nine months to eight years. There is no difference in regard to sex.

The tumors, for the most part, are very large, smooth, or rather irregular or nodular, and are rather soft in consistence, especially when degenerative changes have taken place. On section they show a rather dense capsule, and the character of the cut surface varies in appearance corresponding to its constituent elements. Areas of softening and cysts are quite frequent. Where myxomatous tissue occurs the tumor has a soft, jelly-like consistence. According to Garceau, the growth arises in the parenchyma, and does not infiltrate the kidney tissues as an ordinary malignant growth does, and it seldom involves the pelvis, the ureter, or the bloodvessels. The capsule of the tumor seldom ruptures, and the tumor is rarely adherent to the surrounding tissues. Extension into the renal veins may occur, and even direct invasion of the vena cava, but is not as common as in other malignant tumors. The tumors grow very rapidly, and may reach an enormous size in a very short time, in some cases filling almost the entire abdominal cavity. Weigert has described the only case of multiple mixed tumors, which occurred in the kidney of a stillborn child, and gave the appearance of atypical tubules of epithelium, growing principally between the kidney pyramids and ending in atypical glomeruli.

Metastases are rather uncommon. Walker[6] found metastases in 55 of 142 cases. Garceau found metastases in 21 per cent. of the cases. Metastases are most apt to occur when the tumor is large and has broken through the capsule. They are rarely present when the growth is small.

The tumors are composed of various tissue elements, which usually are quite independent of each other. These elements grow with varying degrees of rapidity, the connective-tissue elements generally predominating. These

[1] *Berl. klin. Woch.*, 1902, vol. xxxix.
[2] *Lectures on Surgical Pathology*, London, 1853.
[3] *Virchow's Archiv*, 1888, vol. clviii.
[4] *Deutsch. Zeit. f. Chir.*, 1886, vol. xxiv.
[5] *Virchow's Archiv*, 1899, vol. clv.
[6] *Annals of Surgery*, xxvi, 554.

tumors are composed of two or more of the following structures: epithelial cells lying either in tubular arrangement or in irregular masses or "pearls," which freely anastomose; connective-tissue cells, sarcoma-like in appearance, and of the round- or spindle-cell variety; myxomatous tissue; smooth and striated muscle; cartilage; bone; fat; and two authors have mentioned a neuro-epithelial tissue. Connective tissue is the predominant feature, forming the framework in which the other tissues lie, and may so predominate as to lead to the diagnosis of pure sarcoma unless careful search is made from various parts of the tumor mass. Ribert states that there are no true sarcomata of the kidney occurring in children, but that all such cases should be regarded as mixed tumors. Smooth muscle tissue sometimes forms a large amount of the tumor substance, and is at times interwoven very closely with the connective tissue. The striated muscle is of less frequent occurrence than smooth muscle, but has been found in 25 per cent. of the cases studied by Walker and in 42 per cent. of those studied by Garceau. Cartilage and fat are found mostly in old tumors, and are rather infrequent. Bone is but seldom found, while neuro-epithelial elements have only been described in two cases, one each by Ribbert and Busse.

The epithelial structures when present are of varying types. They may occur as tubular or glandular structures, the tubules being lined by epithelium of cuboidal type, and arranged in from one to three layers on a basement membrane. The tubules may form lobules separated by connective-tissue strands; at other times the epithelial cells lie in irregular groups or masses, which freely anastomose with one another. In the centre of these epithelial nests the so-called epithelial pearls and cartilaginous tissue is found.

Symptoms.—The presence of a tumor mass is the earliest symptom in the majority of these cases. These tumors lie in the affected area, show a very rapid growth, and sometimes attain a tremendous size. Hæmaturia is rather uncommon, and only occurs probably when the mass invades the pelvis of the kidney, which is rather late and rare. The tendency of the tumors to remain encapsulated renders hæmaturia a rather unusual symptom. Pain is uncommon and occurs late in the disease, the symptoms mainly being referable to the pressure of the enlarging mass. Late in the disease emaciation and rapid loss of weight occur. The duration of the disease is usually less than a year from the onset of the first symptom noted.

Diagnosis.—A rapidly enlarging tumor mass in the kidney area with early emaciation and cachexia in a child is the symptom most characteristic in this disease. Hæmaturia occurs late and is infrequent. The methods for differential diagnosis are similar to those already described under hypernephroma.

Treatment.—Early diagnosis and prompt surgical intervention offer the only hope of cure. The percentage of operative recoveries has much improved in recent years, but the ultimate outlook is extremely gloomy, as recurrences have occurred in all but three of the operative cases noted.

Benign Tumors.—These include adenoma, angioma, lipoma, fibroma, and myxoma. The adenomata have been described. Angiomata are generally small and lie beneath the capsule. They may, however, vary in size from that of a pea to that of a walnut, and are occasionally seen in the medulla. Lipomata are also rare, and usually lie beneath the capsule. One

case of lipoma the size of a child's head has been reported. Fibromata are usually minute and are found in the cortical portion, but are sometimes seen in the medullary portion. One case in which the tumor weighed twenty pounds is reported.

Symptoms.—There are none unless the growth is large. Hæmaturia is very rare. Pain may occasionally be present, but is usually very slight, although it may be very severe if the tumor is large. In such cases symptoms produced by pressure may also be present. The *diagnosis* is usually made when the tumor is large and operation is generally indicated. Unless one can be certain as to the non-malignant character of the disease, it is best to perform nephrectomy, although in certain cases partial nephrectomy may suffice to completely extirpate the tumor.

Tumors of the Pelvis of the Kidney.—These growths are very rare, more frequent in men than in women, and occur between the ages of forty and sixty. They are usually of two forms, a papillomatous and a flat, non-papillary form. The papillomatous forms are the more frequent and are very similar in character to the papillomata occurring in the bladder. Albarran has been able to collect 18 cases from the literature. In one case the papilloma grew down the ureter and subsequently invaded the bladder. Of the non-papillary forms, only 13 cases could be collected by Albarran. These are described for the most part as alveolar epithelioma. A squamous-cell carcinoma of the pelvis is exceedingly rare, one case having been described by Albrecht.[1] Although the histological character of some of these tumors of the pelvis is not malignant in appearance, they, however, are to be classed as malignant tumors. Stone in the pelvis of the kidney has been mentioned as an exciting cause of these growths. There is no definite symptomatology, hæmaturia, which is apt to be profuse, being about the only symptom present early in the disease. Attacks of pain from the passage of blood clots are apt to occur, and in the papillary form pieces of tumor are occasionally, but rarely, found in the urine. The *diagnosis* is usually made as a result of surgical exploration. The *prognosis* is grave. In the nine cases reported by Garceau, recurrence followed in seven, either as distant metastases or in the scar of the wound. The *treatment* is excision—complete nephrectomy.

[1] *Archiv f. klin. Chir.*, 1905, lxxvii.

CHAPTER XIV.

URINARY LITHIASIS: RENAL AND URETERAL CALCULI.

By HUGH HAMPTON YOUNG, M.D.

Definition.—Primary renal calculi may be defined as masses of urinary salts deposited in an amorphous or crystalline form, in and about an organic nucleus and held together by an organic matrix. For the most part they presuppose a diathesis in which certain inorganic salts (the middle and not the end products of catabolism) are supplied in excess to the kidneys for excretion; precipitation of such salts in the pyramids of Malpighii, consequent trauma to the tubular parenchyma in its attempt at elimination, and a urine in process of formation of a composition such as will find difficulty in dissolving out the precipitated salts and prove favorable to their further precipitation subsequently in the kidney itself, the renal pelvis or bladder. Certain inorganic calculi form by precipitation of salts into necrobiotic tissue.

Classification.[1]—Primary calculi are renal in origin, but the secondary calculi may form in any part of the urinary tract. We may distinguish calculi, according to the number present, as the "solitary," or "lone," and the "multiple," and according to their position as renal, pelvic, ureteral, etc.

According to their composition they may be classified as: (1) The organic, of uric acid and its salts, calcium oxalate, cystin, xanthin, and urostealith. (2) The inorganic, consisting of the phosphates of lime and magnesium, and the carbonate of lime.

According to origin they may be classified hypothetically as:

1. "Of crystalline origin," when they may be primarily resultant from irritation of the renal tubules by crystals.

2. "Of necrobiogenic origin," when their first cause may be degenerated renal epithelium, which invites calcification.

3. "Of microbic origin," when their starting point is infection of the urinary tract with urealytic microörganisms.

Secondary calculi, which are common to all dilatations of the urinary tract, may form in the renal parenchyma itself or in the renal pelvis, and thus come under the designation "renal calculus." The conditions necessary for their formation are: (*a*) An infection of the living tissue, with a urealytic microörganism (proteus bacillus, certain staphylococci, etc.), with consequent inflammation, the freeing of ammonium carbonate and the appearance of pus in the urine, and (*b*) obstruction to the outflow of urine causing a stagnant pool in which a slimy mucoid matrix, composed of pus cells gelatinized by ammonia, may rest long enough to allow of sufficient infiltration with ammonium magnesium phosphate to produce solidification. In

[1] Léon Sourdille, La lithiase rénale primitive. *Arch. génér. de chirurgie*, September, 1907. Roy, La gravelle phosphatique primitive, *Thèse*, Paris, 1898.

pyonephrosis one finds this slime infiltrated with phosphates in every degree of consistency in freshly voided urine. The essential salt of this secondary calculus is ammonium magnesium phosphate, the formation of which in the urine is dependent on the addition of free ammonia to unite with the normal magnesium phosphate. Calcium phosphate and ammonium urate are also common constituents of this stone. The so-called "fusible calculus" is composed of ammonium magnesium phosphate and calcium phosphate.[1] All phosphates tend to be friable in consistency and white to gray in color.

Composition of Primary Calculi.[2]—By far the most common are the mixed stones of urates[3] and calcium oxalate in varying proportions and usually in layers in which one or the other salt predominates sufficiently to reveal on section more or less complete concentric rings. Frequently calcium phosphate and sometimes calcium carbonate or even cystin add a layer or more. Either the urates or oxalate may be lacking in these mixed stones, but they are most commonly associated. The phosphates and carbonate of lime are usually found together in the inorganic stones. Very rarely, if ever, do any of these salts form the sole constituent of a calculus. Should an ammoniacal infection supervene on these primary calculi they become invested with triple phosphates, and henceforth further growth is due to phosphates and carbonates alone.

If the outside primary layer of such a stone is composed of urates, a transitional ammonium urate layer intervenes between it and the phosphates, due to the ammonium of the urine combining with the uric acid of the primary calculus. Prout held that such a transitional layer of ammonium urates also occurred when a triple phosphate layer was enveloped by urates, but this must be a very uncommon occurrence.

Such methods of quantitative chemical analysis of calculi as had been used until quite recent years were so inexact that they sometimes furnished misleading information. Recently chemical analyses have been made by Morris,[4] Israel,[5] and Johnson.[6]

Physical Characteristics.—The physical characteristics of calculi vary greatly, and are somewhat indicative of their composition. On these, rather than on chemical analyses, have been based many statements as to the nature of renal calculi. The so-called uric acid gravel is formed of fine reddish, hard granules like cayenne pepper and sometimes of a size up to that of a pea. These are most commonly seen as precipitates in acid urine which has been standing for some time.

The hemp-seed gravel is similar, but of a dark gray or black color. Its chief constituent is calcium oxalate.

Phosphatic sand occurs in "alkalinuria" as white masses of amorphous calcium tribasic phosphates; or in cystitis as secondary white crystalline,

[1] Prout, *Diseases of the Urine*, London, 1821.

[2] The major portion of this chapter, comprising the etiology and composition of calculi, has been written for me, after a most laborious study of the literature, by Dr. George S. Gordon.

[3] So much confusion exists in the literature as to the various salts of uric acid which enter into the composition of stone that the term "urates" is here used to include uric acid and all its salts.

[4] *Surgical Diseases of the Kidney and Ureter.*

[5] *Chirurgische Klinik der Nierenkrankheiten*, Berlin, 1901.

[6] *New York Medical Journal*, 1905, lxxxi, 209.

triple phosphate with an admixture of calcium phosphates and ammonium urate in a slimy mucoid matrix.

The most infrequent, nearly pure, calcium dibasic phosphate calculus is generally of the size of a small pea, cuboidal, with rounded edges and angles, grayish in color, smooth of surface, hard, and with a crystalline fracture.

Multiple oxalates are very like these calcium dibasic phosphate calculi; they, too, are apt to be definite in composition.

The "mulberry stone" of calcium oxalate is tuberculated, stained blackish by altered blood, very hard, and of varying size up to that of a walnut or over.

The "pebble" of urates is of similar dimensions, oval, of sandy surface, medium hardness, and grayish to reddish from admixture with urinary coloring matters.

"Staghorns," or "coral calculi," are of the same materials, *i. e.*, urates (Osler), color, consistence, and surface appearance, but of size and shape like a mould of the renal pelvis. Fagge says they are "always composed of mixed phosphates."

The "jackstone" calculus, of the shape its name implies, of brownish to blackish color and hardest consistency, is another form of oxalate (Fowler[1]).

The xanthin calculi are "of a pale yellow color and exhibit a waxy lustre when rubbed" (Adami[2]). "They vary in size from that of a pea to a hen's egg" (Emerson[3]).

A cystin calculus is hard, oval, light amber in color, glistening of surface, rough, and granular, but non-crystalline, and resembling small masses of amber stuck together without definite arrangement (Fowler).

Urostealiths are "in the moist state soft and elastic at the temperature of the body, but in the dry state they are brittle, with an amorphous fracture and waxy appearance" (Hammarsten[4]).

Calcium carbonate calculi "have mostly chalky properties and are ordinarily white" (Hammarsten). "Naunyn differentiates two forms in man, the one brown and spicular, the other pale and smooth, but of relatively great hardness" (Adami).

Nucleus.—This is usually a solidified agglomeration of the same salts of which the calculi are composed, and forms the core. It differs from sediment inasmuch as it has a colloid matrix, and on the other hand from stone in not being laminated. It originates in the renal tubule, which is the only part of the urinary tract of small enough calibre to retain so small a body.

As it increases in size it erodes the renal tissue, and if this takes place toward the renal pelvis it frees itself ultimately into a calyx, where it may unite with other similar nuclear forming material and become gravel or stone, pass on to lodge in the renal pelvis or other portions of the urinary tract for further developments, or be voided in the urine.

Esbach[5] says that a primary phosphatic nucleus is always replaced by oxalates or urates if they afterward envelop it. Tuffier[6] has demonstrated

[1] *Johns Hopkins Hospital Reports*, 1906, vol. xiii.
[2] *The Principles of Pathology*, 1908, vol. i.
[3] *Clinical Diagnosis*.
[4] *Physiological Chemistry*, 1908.
[5] *Les Calcules Urinaires*, Paris, 1885.
[6] *Étude sur la chirurgie du Rein*, 1889.

experimentally that foreign bodies, unless they can supply an organic material for urinary contents to lodge in, do not form nuclei. Bilharzia eggs are said by Fagge to form the nuclei of uratic calculi in Egypt. Blood clots sometimes form the core of a stone. Fullerton, basing his opinion on the analysis of seven calculi, holds that bacterial agglomerations do not form nuclei. Inorganic calculi usually lack a nucleus, unless formed about a foreign body.

Size.—The size of calculi varies from that of fine gravel to the limit imposed by their enveloping-tissue bed. As the result of abnormal back pressure due to interference with the outflow of urine or to erosion of tissue by the growing calculus itself, a stone may be even larger than any normal expansion of the urinary tract.

Form.—The forms assumed by calculi are dependent on their composition, the shape of their nucleus or nuclei, pressure from contiguous stones (in which case they become faceted), the conformation of the tissue bed in which they form, and on the way the urinary stream impinges on their surfaces to add fresh laminæ or erode, according to whether the urinary contents favor growth or disintegration.

Color.—Calculi are composed of colorless crystals and matrix. Their varying tints come from the urinary pigment, uroerythrin (Adami), or from blood pigment, and vary as these vary in affinity or amount in the urine. When urates form, urinary pigments are much more in evidence in the urine than when phosphates or cystin calculi form, and consequently are more apt to be colored. Oxalates, if of coarse surface, erode into the vascular layer of the urinary tract, and blood pigment stains them. Smooth oxalates are whitish. Cystin calculi may change color on exposure to the air, probably because they contain urobilinogen.

Number.—Probably no calculus forms from a single salt-impregnated renal cast, but about an agglomeration of such. Multiplicity depends on the coalescing of such infarcts either in situ by erosion into neighboring tubules or after expulsion into a calyx. The adhesiveness of the mucoid matrix would vary with the amount of salts it contains, and if it is saturated it tends to form the nucleus of a stone by itself; while if it is in a more glutinous condition and comes in contact with similar infarcts, fusion would occur. In the first instance multiple stones would form, and in the second a single calculus. If this hypothesis be correct there would hardly be a limit to the number of calculi forming in a kidney, and such is the case. On the other hand, many of these nuclei would escape in the urine before attaining size enough to prevent their exit. Of the "lone" calculi, the most common are the urate "pebble" and the oxalate "mulberry."

Bilaterality.—Holt,[1] after 1000 autopsies on infants, states that granular deposits are generally seen in both kidneys. Lagueu[2] holds that in one-half of the cases where calculi form in one kidney the other is similarly affected. Albarran[3] considers the frequency of stone on both sides as an argument in favor of the systemic origin of calculus. Given that the formation of calculi is a result of imperfect catabolism, the "crystalline diathesis" so-called, one would always expect to find both kidneys the resting place of calculi in certain conditions, but for the fact that stone-forming material escapes in the urine very often before it has attained sufficient size to be retained.

[1] *Diseases of Infancy and Childhood.*
[2] Les calcules du rein et de l'uretère, *Thése*, Paris, 1891.
[3] *Lancet*, 1892, i, 1345, 1339.

Disintegration of Calculi.—Adami, speaking of uric acid stones, says: "The evidence seems to be conclusive that through keeping the urine alkaline through long periods by giving sodium bicarbonate, alkaline soaps, etc., not merely is gravel arrested, but the stones within the bladder after such treatment show clear evidence of erosion. . . . In examining any large collection of uric acid calculi obtained in the postmortem room, etc., certain specimens have a ragged, worm-eaten appearance, and upon section are found loose in texture, with evidence of lamination very indistinct." Rovsing says, "Colon bacilli can permeate the strata of calculi and cause them to crumble away" (Morris).

A meat diet, tending to render the urine acid, might cause disintegration of a primary phosphate stone; while urotropin or the introduction of colon bacilli or other acidophyle microörganisms (were such a procedure feasible), by destroying urealytic microörganisms, might render the urine sufficiently acid to disintegrate a triple phosphate calculus. The oxalate being found in acid, neutral, and alkaline urines cannot be affected by treatment by acids or alkalies.

Etiology.—Age.—Calculi are found in the kidney throughout life, but are very rare in old age. Fry and Martin,[1] in a study of 100 hospital infants under the age of three months, found an abundance of uric acid in the voided urine of 26 of them, of whom 19 died, and in 7 of these autopsies were done which demonstrated uric acid infarcts in the apices of the pyramids. Holt says, basing his remarks on 1000 autopsies, that "small renal calculi are very common in infancy," but that they are usually voided during the first two years of life. He found one large renal calculus. By far the greater number of clinicians hold that renal calculus is rare in early life, but in the light of these figures they are evidently at fault. Calculi in the kidneys are most in evidence about the fourth decade. To this period belong the urate infarcts of the gouty and the calcium oxalate stone. Osler refers to the calcium phosphate infarcts of old age. Old people are not so prone to stone in the kidneys, because a "crystalline diathesis" declares itself, if at all, before this period, and the patient has passed all his calculi (at least as far as the bladder), had them removed by operation, or has a ureter sufficiently dilated, by the previous passage of stone, to offer no obstruction to the passage of calculi to the bladder. Stone is said to be common in poor children and rich adults.

Sex.—That renal calculi occur more frequently in men than in women is generally accepted, but there do not appear to be statistics showing the relative frequency in the two sexes. Giraldes held that vesical calculi in females never formed except when a foreign body had been introduced, but this does not obtain with renal calculi. Small renal calculi which pass into the female bladder are easily voided, but the same anatomical structures tend to hold them in the kidney in the female as in the male.

Heredity.—Heredity predisposition, the "péché original" of D'Etiolles, is almost universally admitted, and many authorities hold that urate gravel ranks as an evidence of gout. Oxalates and xanthin are so closely related to urates that they may be fathered by the same etiological factors. Cystinuria and a tendency to form cystin calculi also "run in families."[2]

[1] *Transactions of the American Pediatric Society*, 1903, p. 150.

[2] Fowler, Cystinuria, etc., *Johns Hopkins Hospital Reports*, 1906, xiii.

Amorphous phosphaturia is often associated with neurasthenia, and suggests the transmission of an unstable nervous system from father to son.

Occupation.—"Sedentary occupations seem to predispose to stone" (Osler). D'Etiolles held that exercise was the "bellows blowing," which gave a good intake of oxygen through the lungs and thus secured combustion of tissue waste, and statistics and observation bear out the theory that stone formation is generally dependent on occupation only so far as the occupation is an active or sedentary one. Those engaged in plumbing and who use alcohol in excess are predisposed to renal calculi as to gout. Hutchinson called attention to the freedom of sailors from stone and attributed it to their salt diet, but D'Etiolles states that naval officers, notwithstanding that they also ate an excess of salted food in his day, were as prone to calculi as others, and instances the famous Dutch Admiral de Ruyter. Civiale's list[1] of prominent men, "victims of the sharp and craggy stone that cruelly pricks and tears," includes, among others, Cromwell, Bacon, Boerhaave, Louis XIV, George IV, Napoleon I, Peter the Great, Montaigne, Newton, Horace Walpole, Fothergill, Hartley, Harvey, Mascagni, and Scarpa.

Diet.—How absolutely unestablished is the etiology of calculi could be no better demonstrated than by noting the discord of deductions drawn by eminent authorities in the attempt to inculpate diet as causative. Cadge and Dickinson held that hard drinking water was the cause of stone in Norfolk. Denny thought absence of lime in drinking water caused stone in Holland. A. E. Roberts[2] holds that stone in India is uncommon among those natives whose food contains sodium chloride, and Hutchinson believed that sailors were exempt from stone because of their salt diet. Yet Morris says that "salted meats are inducive of renal concretions," and D'Etiolles held that naval officers, who in his day ate much salt food, were especially subject to stone. Sir Wm. Roberts[3] and many others maintain that ingested oxalic acid is a cause of oxalate calculi, yet Chabrié lived on food rich in oxalates for a month and never succeeded in finding oxalates in his urine. Such instances of various opinions might be multiplied indefinitely.

If the theory so well put by Futcher,[4] "that owing to some organ or organs failing to produce a ferment (which normally is necessary for the proper destruction or oxidation of uric acid) oxidation of uric acid does not occur, and consequently accumulates in the blood in excess," is correct, then the ingestion of food rich in nucleins would cause an excess of uric acid and possibly xanthin to be presented to the kidney tubules for excretion; and this is a prime step in calculus formation. Exclusion from the diet of nucleins would cut off this supply of calculous material.

There is now a consensus of opinion (Guyon, quoting Chabrié, excepted) among physiologists, pathologists, and clinical observers that ingested oxalic acid appears, at least, in part, unchanged in the urine. It does not seem improbable that, as demonstrated by Dickinson and Roy, the drinking of lime water furnishes one of the bases for inorganic calculi. The writer has been recently informed that the drinking water of Holland contains lime. Adami says that diet influences cystinuria in no way.

Distribution.—Stone is common in the cold as in the warm climates, in the moist as in the dry, in the highlands as in the lowlands, inland as well as in

[1] *Traité de l'affection calculeuse*, Paris, 1838.
[2] *Lancet*, 1895.
[3] *Ibid.*, 1892.
[4] This work, vol. i, p. 824.

countries bordering on the sea. It is common in Iceland. There are "stone districts" in England (Norfolk, Bristol, etc.), the west of France, about Moscow in Russia, some parts of Germany, in lower Egypt, in the uplands of India, and in Holland. In America stone is fairly evenly distributed and favors no particular locality. Norway, Sweden, and Styria were said by Roberts in 1866 to be practically free of stone. Whatever the cause may be, residence in certain districts is said to confer a tendency on visitors to the formation of stone, which they lose on leaving (Fagge).

Previous Disease.—Almost every form of disease is referred to by authorities as causative of renal calculi, and it would be strange indeed if each of them had not been at one time or another the precursor of stone. Their etiological relation is not at all proved except in the following ailments, whose role has been more or less fully substantiated clinically or by physiological experiment.

1. Those diseases which interfere with the complete combustion of food or tissue waste into urea and permit of the circulation in the blood of an excess of uric acid, oxalic acid, xanthin, or cystin. These tend to form organic stone in the kidney. Such diseases are: (*a*) Intestinal disorders which allow the toxic mid-products of mucosal enzyme digestion, such as albumoses, etc., to reach the liver and by affecting it produce "hepatic incontinence." (*b*) All liver diseases which interfere with its urea-forming function; especially to be noted is hepatic cirrhosis. (*c*) Lung disease which limits the intake of oxygen. (*d*) Cardiac and arterial diseases (whether or not produced by alcohol or lead), which do not allow of sufficiently free circulation to permit the blood to be well oxygenated. (*e*) Gout. (*f*) Disease which may supply an excess of uric acid to the kidney without the necessity of its passing through the liver, such as leukæmia.

2. Ailments which produce a fatty degeneration of the renal tubular epithelium, such as (*a*) the above diseases which are accompanied by crystalline deposits in the kidney causing fatty degeneration, (*b*) fevers, and (*c*) obesity.

3. Fagge attributes at least some of the frequency of stone in Egypt and Natal to Bilharzia eggs in the urinary tract, which provide a nucleus for the deposition of urinary salts.

4. Diseases characterized by renal hemorrhage, such as hæmophilia and tuberculosis. The hemorrhage supplies blood clot, which acts as a nucleus.

5. Oxaluria has been found in certain forms of dyspepsia of a somewhat neurotic type in confirmed obesity and in association with diabetes (Adami).

6. "Alkalinuria" is due "first to a diet which raises the alkalinity of the blood, as a vegetable one, in gastric diseases with considerable loss of hydrochloric acid to the body through hypersecretion with motor insufficiency and vomiting or lavage, perhaps diarrhœa, also and especially as a symptom of neurasthenia (Peyer), without any of the above-mentioned causes. In such a case during a period of neurasthenia a diminution in the phosphoric acid to about half and an increased calcium output have been found. The nitrogen was also decreased. It seems to be excessive calcium, relative to phosphoric acid, which leads to precipitation. It occurs in persons also after sexual excesses and in the depression following psychical exaltation, in which case the cause is not known, but a nervous control suspected. It is often found among mental cases (Heinicke)" (Emerson).

Fullerton states that microörganisms do not form the nucleus of stone,

although they may be present in the layers surrounding it. Thus, it would seem that the bacilluria which so often accompanies and follows typhoid fever for so long a period is not especially likely to be the forerunner of calculus.

Secondary calculi of ammonium magnesium phosphate and other secondary salts follow local infection, such as is especially liable to supervene on spinal paralysis.

Hypotheses of the Etiology of Calculus.—Prout, in 1821, in his classic monograph on *Diseases of the Urine*, gave as causes of excess of lithic acid in the urine, (*a*) simple errors of diet, (*b*) unusual or unnatural exercise of the body or mind, particularly after eating, and the want of proper exercise at all other times, and (*c*) debilitating circumstances.

Sir Wm. Roberts says, "There is perhaps too ready a disposition to look for the determining causes of gravel elsewhere than in the urinary function, in the stomach or in the liver, or in some constitutional vice." The weight of physiological, pathological, and chemical evidence favors Prout's statements of almost one hundred years ago as opposed to this view of to-day. Roberts admits that "there is, however, no doubt that there exists a special relation between uric acid gravel and gout," which he says results from an error "this side" of the kidney, while in the former the error is on "that side."

Bence Jones,[1] in 1850, said: "It has been stated that urine possesses vital properties." Does metabolism of the urine itself cause stone? Urine is merely nitrogenous material, mineral salts, and coloring matters held in solution. In bacilluria, in which, perhaps, one might best maintain the function of the urine as that of a living tissue protecting the organism from general infection, Geraghty[2] among others has demonstrated that the urine is merely the recipient of germs from other sources, and that they multiply so profusely as to indicate that nothing holds their growth in check. In such cases, with a urine ideally ammoniacal, even triple phosphates will not form stone, but are voided as a dense precipitate.

If then not a living tissue, can urine change its character in the urinary passages "that side" the kidney and form stone there? Sir Wm. Roberts says all uric acid in the tissues or urine is normally in the form of soluble quadriurates, $QU(MHUH_2U)$, a definite chemical entity; that when the urine contains an excess of acid and QU and a lack of salines and coloring matter the sodium acid phosphates, NaH_2PO_4, abstract the metal from the QU, and by double decomposition precipitate the slightly soluble uric acid, H_2U, and sodium acid urate, MHU. These may form stone in the renal pelvis or bladder, but admitting his theory to be correct, whence come this excess of QU and acid and the lack of salines and coloring matter? They vary in quantity with the power of the kidneys to produce or excrete them. Admitting that urine may have the power to form stone "that side" of the kidney, this power is manifestly dependent on material derived from the kidney, and holds good for urine in the renal tubules as well as in parts of the urinary tract distal to them.

Is it necessary to go farther than the "urinary functions" to determine the cause of gravel? In other words, can the kidney act independently of other glands and tissues and elaborate material for stone without regard

[1] *Animal Chemistry*, London, 1850.
[2] Persistent Bacteriuria, *Johns Hopkins Hospital Reports*, 1909, xx, 12.

to what abnormal or normal metabolism provides for it? We think it cannot. Removal of the testes produces atrophy of the prostate. Removal of the parathyroids causes tetany. The myxœdematous lack the thyroid. Injection of renal blood into the portal vein greatly increases urea in the urine (Tessier), and so on. Sufficiently pertinent facts are known to indicate that no gland or tissue acts independently of other tissues even in disease. Moreover, excretory glands to functionate properly depend on other tissue to put ideal end products of metabolism into the blood stream. Almost all nitrogenous waste (whether of food or tissue) is normally excreted by the kidney as urea, yet experiments show that the kidneys cannot produce urea from even so closely allied a substance as ammonium carbonate. Experiments with Eck's fistula, etc., demonstrate that for the most part it is the liver which normally takes from the nitrogenous elements ingested the part that is not to be used as food and reduces it to exogenous urea. It is for the most part the liver which also elaborates the waste tissue products brought to it in the blood stream into endogenous urea. Were all the waste products of nitrogenous metabolism reduced to urea, H_2O and CO_2, no uric acid, urate, xanthin, oxalate, or cystin calculus would form in the urinary tract, and these are all of the organic calculi.

Let us now consider:

1. The reaction of the urine in its relation to all forms of calculi.
2. Crystallization of the urinary salts.
3. The hypothetical origin of such salts.
4. The hypothetical origin of the matrix of calculi.
5. Distinctions between sediment, gravel, and calculi.
6. Formation of calculi.

1. **Urinary Reaction.**—In its relation to the formation of calculi: Uric acid crystals occur in acid urines and dissolve on the addition of caustic alkali.

Acid urate crystals occur in acid or neutral urines.

Alkaline urate crystals occur in urine rendered neutral by fixed alkalies.

Ammonium urate crystals are only characteristic of ammoniacal urines, but also occur in neutral urine.

Calcium oxalate crystals occur in acid, alkaline, and neutral urines.

Calcium carbonate crystals occur in alkaline urine and dissolve with effervescence on the addition of acetic acid.

Calcium phosphate (amorphous), $Ca_3(PO_4)_2$, occurs in alkaline urine and dissolves without effervescence on the addition of acetic acid.

Calcium diphosphate crystals ($CaHPO_4$) occur in neutral or faintly acid urines, and dissolve on the addition of dilute acids.

Magnesium phosphates (amorphous), $Mg_3(PO_4)_2$, occur in fixed alkaline urine.

Magnesium phosphates (crystalline), $Mg_3(PO_4)_2 22H_2O$, are very rare in human urine.

Cystin occurs in acid urine (Fowler, Prout, von Eberts).

Xanthin crystals are soluble in ammonia (Emerson).

Ammonium magnesium phosphate crystals occur in ammoniacal and amphoteric urines.

2. **Crystallization.**—As the forms of crystals may have to do with the production of matrix material, the more spiculated being more irritating would produce more tissue degeneration, and thus perhaps more irregularly shaped

nuclei. Once embedded in their matrix their forms are modified, as shown by Orde, and probably no longer have to do with the general outlines of calculi, only inasmuch as they may or may not supersaturate a nucleus to such an extent that it will not adhere to other nuclei.

Of the urates, we know that uric acid crystals are normally rhombic in form, but its salts as found modified in urine are amorphous, round, thorn-apple, and whetstone shape. They may be in clusters or single, and are stained yellow to brownish red with urochrome, urobilin, or uroerythrin.

Calcium oxalate is normally octahedral in shape, and is found in such form in the urine, but it may become dumb-bell-shaped as well.

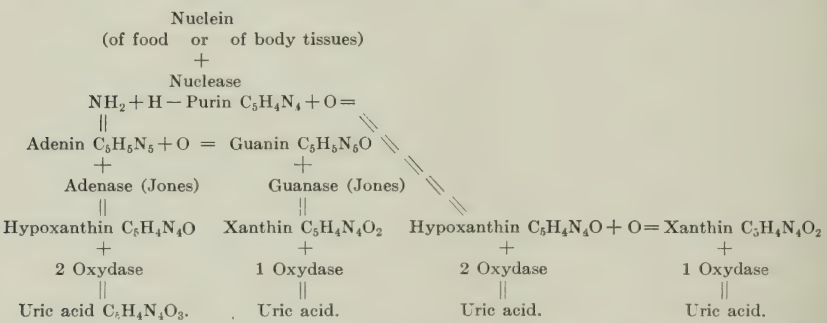
Cystin crystals are sexangular plaques, and are unmodified in the urine.

Calcium phosphate crystals are normally slim wedges, and are found in the urine as such, but are usually amorphous or perhaps in yellowish (bile stained) sheaves of microscopic needles (Boggs), and occasionally one sees these wedges crossing each other, or in clusters.

Calcium carbonate crystals usually appear in the urine as amorphous masses, or they may assume somewhat the shape of the oxalate dumb-bell or of large, concentric, radiating spheres.

Xanthin crystals normally are sexagonal, elongated plates, and in the urine "resemble uric acid somewhat" (Emerson). The triple phosphates belong to the normally rhombic crystalline group. In the urine they appear as such, the so-called "coffin lids," or modified into more or less crucial-shaped, feathery forms.

3. **Origin of Uric Acid.**—Emil Fisher's genealogical tree of uric acid is:



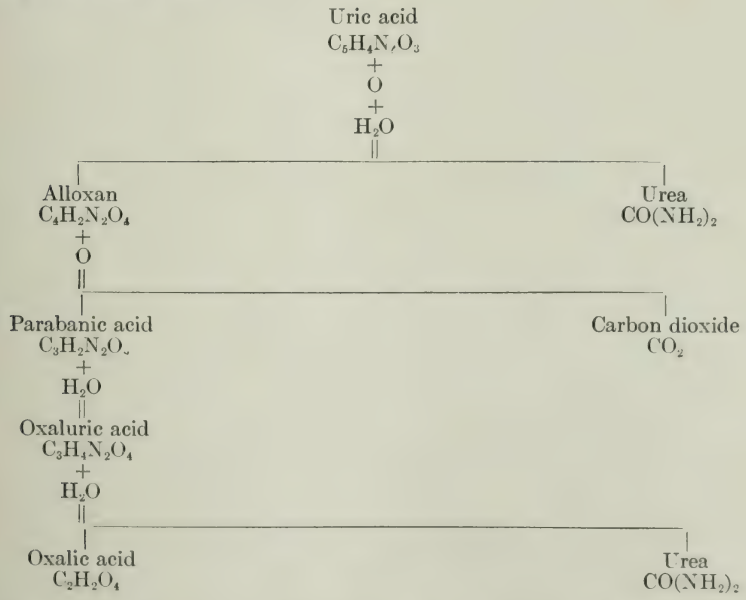
(The further steps in the reduction of uric acid to urea can be seen on consulting the oxalic acid genealogical tree.)

All the uric acid which passes through the liver is normally converted into urea by a urocolytic enzyme, but about one-half of the endogenous uric acid escapes the liver, and this is excreted normally unchanged by the kidneys. It amounts to approximately 0.7 gram per day. "We do not know in what form uric acid exists in the circulating blood." Sir Wm. Roberts considered it as the quadriurate $MHUH_2U$ when in solution. When in excess it deposits in the renal pyramids as amorphous or crystalline bodies like tophi in the ear or chalk stones. Excess of uric acid supplied to the kidney for excretion may be due to: (1) Failure of the liver to produce sufficient uricolytic enzyme to transform uric acid into urea, or (2) excessive formation of endogenous uric acid which can short-circuit the liver, as it were, in reaching the kidney.

It does not seem likely that the liver is solely at fault in these diatheses, although it is held that the kidney is "more sinned against than sinning" when stones form. The fault may be one mainly of the liver, still the liver in its turn may have its handicap thrust upon it by gastro-intestinal disturbance, diseases of the lungs, leukæmia, anæmia, cardiac disease, etc. Moreover, other tissues than the liver may be responsible for combustion of waste products and their default be the main cause of calculus formation, but this seems very unlikely. In leukæmia the uric acid from the nucleins may reach the kidney in very considerable quantities, unaffected by the liver metabolism. Since injection of blood from the renal vein into the portal vein will cause increased urinary excretion of urea, it would seem not unlikely that calculous deposits with their associated chronic nephritis may lessen the amount of an internal renal secretion, which, in turn, lessens the uricolytic enzyme production in the liver, thus forming, as it were, a vicious cycle.

Origin of Xanthin.—Another of the mid-products of metabolism which furnishes the salts for renal calculi is xanthin—Emil Fischer's dioxypurin (see uric acid genealogical tree). This is merely uric acid less one atom of oxygen, and that it is so very rarely found in the urine would indicate that it is almost always oxygenated, at least to uric acid, in the body. Still there may be a very small amount of it in normal urine. Its excess would be due to the lack of an oxydase, probably of the liver, or to excessive endogenous formation.

Origin of Oxalic Acid, $C_2H_2O_4$.



Chemically, Simon says, "Oxalic acid may be regarded as a complete oxidation product of uric acid." Oxalate calculi are so often mixed with urates as to indicate as close a relation etiologically as appears in the above scheme, and we find that clinicians, in speaking of causation, have very

often drawn no distinction between the two. Like uric acid, it may be exogenous or endogenous, and "is increased in various diseases in which the oxidation processes are manifestly at fault." On the other hand, pure oxalic calculi, if they exist, would demonstrate that the "oxalic diathesis," recognized by Adami, is independent of "uric acid diathesis." On the other hand, authorities recognize indigestion in neurasthenia as causative of oxaluria; oxalic calculi do not dissolve in alkaline urine; they often have a layer or more of calcium for their base, all of which would seem to indicate some relation to the "alkalinuria" diathesis.

Origin of Cystin.—$C_6H_2N_2S_2O_4$. This salt, so uncommon in urine and the calculi of which are so rare, has been the subject of much controversy and research. Fowler, after passing under review the various theories of its origin, concludes: "Cystinuria, or the presence of cystin in the urine, is, therefore, to be looked upon as an indication of defective proteid metabolism. . . . It is not known in what part of the body cystin is formed, but the suggestion was made long ago that that overworked organ the liver is responsible. We have seen that the recent work of Friedmann lends some support to this view. It remains, however, for further clinical and experimental work to solve the question."

Origin of Calcium and Magnesium Phosphates and Calcium Carbonates.—These salts escape through the urinary tubules as sediment in what Emerson calls "alkalinuria" (the commonly but falsely so-called "phosphaturia"), a condition in which "we are dealing with a diminished acidity, and it seems with a diminished excretion of phosphoric acid and an increased elimination of lime" (Hammarsten). "Recent study of these cases with symptoms of neurasthenia and a phosphatic sediment in the fresh urine would indicate an abnormality in the calcium metabolism—an absolute increase of this with a decrease of phosphoric acid" (Osler). These, however, are the amorphous phosphates, and do not tend to form calculi except secondarily to an aseptic necrosis. In the "phosphatic diabetes" of Tessier, on the other hand, calcium salts never precipitate in the urine. These amorphous phosphates, $Ca_3(PO_4)_2$, the crystalline calcium phosphate, $CaHPO_4$, calcium carbonate, $CaCO_3$, magnesium phosphate (amorphous), $Mg_3(PO_4)_2$, magnesium phosphate (crystalline), $Mg_3(PO_4)_2+22H_2O$, are normally present in the circulation in some form and may deposit in necrobiotic cellular tissue to form the non-nucleated, non-laminated, pure phosphate stone so-called, or layers on an oxalate or other organic calculus. No diathesis to increase the amount of lime in the organism is necessary to explain this. The process is very similar to the calcification of a tuberculous focus. On the other hand, if there be a phosphate and carbonate diathesis in which these salts in a crystalline form are furnished to the kidneys in excess for excretion resulting in degeneration of the renal epithelium, inorganic stone may have the same crystalline genesis attributed to organic calculi.

4. **Origin of the Matrix for Organic Calculi.**—(Urates, oxalates, cystin, and xanthin.) Rainey is said to have been the first in 1858 to call attention to the effects of colloids on crystallization. Orde's classic experiment of crystallizing calcium oxalates in gelatin demonstrated that salts take on bizarre shapes or become amorphous under such conditions. Tuffier found that an aseptic foreign body placed in the renal pelvis of the dog became in time merely frosted with urates and phosphates, and that there was no agglomeration of salts. The colloid cement to hold the crystals together

was wanting. "Poisoning with oxalic acid (Kobert, Kusner, and Newberger) leads to abundant deposits within the kidney of calcium oxalates" (Adami). Ebstein and Nicholaier fed dogs on amide of oxalic acid, and at autopsy they demonstrated not only oxalate of lime in the tubules, but also fatty degeneration of the epithelium. Sourdille says, "The elimination of crystals in the interior of secreting tubules does not take place without wounding the tubules." This is "néphrite lithogene"—a nephritis set up by the crystals which produce a colloid material for organic stone as distinguished from "néphrite lithiasique" or a nephritis the result of calculus in the kidney. Strictly speaking, both forms are due to stone, but in the former only crystals, while in the second calculus itself, is present to cause nephritis.

Origin of Matrix for Inorganic Primary Calculi.—(Calcium carbonate and calcium and magnesium phosphate.) Litten, in 1881, tied the renal artery, and necrobiosis of the epithelium of the renal tubules followed, which formed the matrix for deposition of calcium salts. Dupré found necrosis in the renal epithelium in infants who had been poisoned by Spanish-fly blisters, and calculus followed. The writer has seen a microscopic section of the kidney of a man poisoned with corrosive sublimate which shows the renal tubules stripped of their lining cells and filled with granular deposits, presumably of lime, embedded therein. "Klotz showed that if celloidin capsules filled with fat or a fatty acid be inserted into the peritoneal cavity of a rabbit, in the course of a few days these are found to contain an amount of calcium far in excess of that present in the body fluids of the animal" (Adami). One can hardly avoid the conclusion that intoxication by ingested poison or by disease which would be severe enough to cause necrosis of the renal tubular epithelium would furnish a matrix for calcium and magnesium salts to precipitate in. But some of these salts are also crystalline, and as such, owing to an alkaline diathesis if supplied in excess to the kidneys for excretion, may be capable of setting up a lithogenous nephritis similar to that induced by the organic crystals. Roy holds that the toxines of fevers affect the renal epithelium producing the degeneration, and if such patients are treated with alkalines for a prolonged period inorganic calculi form.

5. **Sediment Gravel and Stone.**—When these salts are washed out of the tubules of the kidney, why do they at one time form urinary sediments, at another gravel, and at another stone? The salts which are excreted as sediment in the fresh urine are, for the most part, amorphous and consequently not so irritating to the renal epithelium as to induce inflammation, with a resultant colloid into which the particles of salt may precipitate—amorphous tribasic, calcium phosphate in "alkalinuria," or perhaps quadriurates in "uraturia." These may continue for years without the formation of true gravel or stone. When, however, urinary salts are massed in a matrix they are said to form gravel. Stone consists of these masses of agglutinated infarcts surrounded by lamellæ of similar or dissimilar salts in a similar matrix. Henry, quoted by Prout, states that primary phosphatic calculi consist of the phosphates alone without a nucleus and without laminæ.

6. **Formation of Calculi.**—We have considered the urinary conditions, reaction, absence of coloring matter, presence of mineral salts, etc., favorable to the formation of stone, the salts and matrix of which they are composed, and their respective origins.

Urine, in process of formation, separated from the blood at the glomeruli, flows through the tubules according to Heidenhain, dissolves out the solid in the tubules, and is in part absorbed; what is left leaves the tubule as the finished product—urine—which thence flows through calices, renal pelvis, etc. Now, if it can dissolve out the salts in the tubular epithelium, but owing to absorption not hold them in solution, and they are amorphous[1] urates or phosphates, it carries them as sediment with probably little or no irritation to any part of the urinary tract. If the salts are crystalline and sufficiently infiltrate their matrix, they may occlude a tubule or more at first, but ultimately be washed out entire or in an agglutinated mass of similar plugs from other tubules forming gravel. Yet again these crystals, forming infarcts, may erode their containing tubule and cement themselves to similar infarcts in neighboring tubules in the kidney itself, may then erode into the calyx en masse, and again form gravel.

They may be retained in the renal tissue still longer, erode into tubules with patent lumina, through which fresh salts may be added to their composition. They may erode in one place into a calyx, yet not free themselves from their kidney bed, and increase in size on the renal pelvic side by deposition from the supersaturated urine, passing their outcropping into the calyx. They may free themselves into a calyx as a nucleus so large as to be voided only with colic or remain to become laminated because of the changing nature of the urine contents in which they are bathed. Once the nucleus is of size to be retained it will be bathed by the products of renal inflammation until the renal cells recover. Thus a matrix for whatever salts may be precipitable in the urine is furnished to supply fresh layers on the calculus. Stones may remain embedded in the kidney for their entire period of existence, but considering that they form in the renal pyramids and have the pressure of urine in process of excretion behind them and the power of necrosis by pressure in front, it is little wonder that they practically always slough out into the calyx, thence to be voided or remain in situ for increasing growth in the calyx, pelvis of the kidney, ureter, bladder, or prostatic urethra. The weird shapes assumed by some calculi are probably due to conglomerations of nuclei or even of stones in their soft or glutinous period, as well as to extrinsic causes, such as the shape of their bed.

Pathology.—Lesions of the Kidney and Ureter.—When the calculus is aseptic the kidney may remain fairly healthy, and there may be no inflammatory complications. Albarran claims that every calculous kidney, although it may appear normal, presents lesions of nephritis, "la néphrite lithiasique." He thinks these alterations are of etiological relation in lithiasis, but, also, that when the calculus is formed the lesions become aggravated as a result of the elimination of salts. This form of nephritis is diffuse, beginning by epithelial lesions, which are soon accompanied by interstitial sclerosis. In the more advanced periods the kidney is retracted and becomes nodular. The capsule becomes adherent, and numerous small cysts are seen. In certain cases, according to Albarran, the kidney is very large and studded with cysts of various sizes, resembling a polycystic kidney. If the calculus obstructs the ureter more or less completely, hydronephrosis develops. This may be associated with marked dilatation of the pelvis and calices, with great thinning of the renal cortex. It has been shown that intermittent

[1] Urates in an amorphous form are rarely, if ever, present in freshly voided urine.

and incomplete stoppage of the ureter with a calculus is much more apt to lead to hydronephrosis than a complete blocking of the urinary outflow. In one of the writer's cases, in which the ureter was completely blocked and five calculi were present, the kidney was markedly contracted and atrophic, forming in reality a fibrous capsule for the calculi. There was apparently no secreting substance left, and no fluid secreted. In some of these cases of contracted kidney the perirenal fat becomes greatly increased, forming a large, fat, tumor-like mass around the kidney. Renal calculi may remain for years without any accompanying bacterial infection, but it is more common to find bacteria present, and they may easily precede or follow a lithiasis. In some cases this infection is of a mild degree, and accompanied only by a slight chronic inflammation of the pelvis and a certain amount of nephritis. In other cases numerous small focal areas of infection are present in the renal substance, and the condition known as pyelonephritis exists.

Albarran has given the term uropyonephrosis to hydronephrosis, which is slightly infected and in which the kidney pelves are only slightly dilated or filled with pus. When the inflammation becomes severe, with extensive abscess of the pelvis of the kidney, pyonephrosis usually results, often associated with great thickening or complete destruction of the cortex and the formation of a large, irregular fluctuating mass. At times the cystic distention involves only a portion of the kidney. This happens particularly in cases in which the renal pelvis is of unusual type, viz., those cases of multiple pelvis or with two or more ureters. In one of the writer's cases there was a large pyonephritic abscess of the upper half of the left kidney, the lower half of the kidney being normal and emptied by a separate branch of the ureter, which joined the other branch about seven inches below the kidney. The cystic distention of the kidney may reach an enormous size. There is often considerable perinephritis, and in some cases the capsule becomes greatly thickened and very fibrous, forming an extensive layer of induration around the kidney, which is sometimes very closely adherent to it.

Number.—The number of stones may vary greatly. In 48 cases operated upon by Israel, only one stone was present in 22, but in 26 there were more than one calculus, the largest number being 36 in one kidney. From one of the writer's patients thirty-four stones were removed from the right kidney and fourteen from the left six weeks later. According to Israel both kidneys are the site of stone in 27 per cent. of the cases, and according to Legueu in 50 per cent. According to the writer's experience both of these figures are too high.

Location.—Calculi are most frequently in the pelvis or in one or more calices. At times they may be embedded in the substance of the kidney, and at others have passed beyond the pelvis into the ureter, in which there are three points at which calculi most commonly lodge. These places are points of natural constriction of the ureter, and lie (1) just below the beginning of the ureter, (2) just at the crossing of the iliac vessels, and (3) in the terminal portion of the ureter. A calculus which has escaped from one of the calices or pelvis into the ureter may stop at any one of these points, or it may pass into the bladder and remain there as a vesical calculus. Not infrequently these are caught at the ureteral orifice, where they produce a fusiform-like swelling or project into the bladder.

Symptoms.—The symptoms of renal calculus are very variable. In those cases which are associated simply with the passage of sand there may be no symptoms at all, but more often there is a feeling of discomfort in the back or region of the kidney, which is relieved by its passage. Not infrequently, however, this sand produces an irritation in the ureter, bladder, and urethra during the passage. When a definite calculus has been formed the symptomatology depends considerably on its location and its movements. Not infrequently there are no subjective symptoms produced, and in one case the disease was present for a period of many years, and the only symptom which attracted the patient's attention was a recent onset of fever followed by pyuria. Yet in this case fourteen large calculi, some considerably larger than a hen's egg, were present. The patient was a very corpulent man. In another case a calculus remained in the ureter for ten years without symptoms after the first attack of colic. Pyuria again attracted the patient's attention, and he was greatly surprised when a calculus four inches long was removed from his ureter.

In a study of twenty-one cases there was a history of pain in 17, and in 13 cases it was of a colicky character, radiating toward the groin and generally into the testicle. Only one was described as radiating to the end of the penis, and in this case several calculi were passed per urethram. The pain is most commonly described as that of a dull, aching character, located in the small of the back on the affected side and sometimes beneath the ribs in front. This pain is generally increased by active exercise, by riding on horseback or in a rough vehicle, and by stooping forward. Most often it is slight in character, although more or less continuous. In a few cases, however, it is severe, and occasionally is present also on the other side of the back. The presence of a reno-renal reflex (*i. e.*, pain referred to a sound kidney from a diseased kidney in which there is no pain) has now been recognized in a sufficient number of well-authenticated cases to warrant the acceptance of this as a rare but definite occurrence. In a recent paper, Johnson has reported two definite cases, and has referred to others, which seem well established; it seems clearly proven that this remarkable symptom must be carefully borne in mind. An apparently clear history of calculus is not, therefore, sufficient to decide as to the kidney involved; the wrong kidney has been operated upon in quite a number of cases. The character of the calculus has much to do with the severity of the pain and the traumatism produced, according to Osgood, who says that a sharp, rough calculus the size of a pinhead may produce the most agonizing colic, while a smooth stone nearly as large as a cherry may remain in the pelvis or ureter throughout life without severe pain. Calculus in the kidney or in a calyx may produce a pain which is referred all along the ureter, and a calculus impacted in the lower end of the ureter may produce a typical colic in the region of the kidney.

Renal colic, which is the most characteristic and most distressing symptom of calculus, fortunately occurs at more or less prolonged intervals. It is frequently ushered in by vomiting, which is soon followed by pain of extreme violence in the lumbar region of the affected side, usually associated with muscle spasm, which causes the patient to double up and frequently to get on his hands and knees. As a rule, radiation of the pain from the lumbar region along the side downward and inward toward the groin and into the scrotum and testicle occurs, causing marked retraction of the

latter. The course of this pain is usually supposed to follow the genitocrural nerve. In some cases it extends also down the ureter into the bladder, and is associated with vesical irritability and frequency of urination; but usually this is rare, except when the calculus has passed to the lower portion of the ureter or into the bladder. An attack of colic may be associated with great systemic depression, chills, fever, rapid pulse, pallor, and severe gastro-intestinal disturbance, and not infrequently persists in its intensity for several hours, until it has been relieved by the use of large doses of morphine. Not infrequently several injections of morphine are necessary to obtain relief, and it is a noteworthy fact that the patient is able to withstand much larger doses during these attacks than at other times. Fortunately, nephritic colic is apt to disappear after the first attack and not to recur for several months, although occasionally it may recur for several successive days and cause great prostration. During or after the attack the urine usually contains a certain number of red blood cells, and occasionally leukocytes; but in some cases both of these may be absent. The cessation of the colic is sometimes due to the successful passage of the calculus into the ureter, and occasionally into the bladder, but most often no calculus is passed, and the cessation of the attack must be attributed to a change in position of a calculus—a stone which has become engaged in the upper end of the ureter may in some way become misplaced.

In this series of 21 cases, colic was present at one time or another in 13, but in only 7 cases was there a history of the passage of a calculus into the bladder and out through the urethra. Owing to the fact that small calculi may not be observed, these figures may be erroneous.

Renal colic is not, however, absolutely diagnostic of stone. It occurs with other diseases in which the ureter suddenly becomes blocked, either by a blood clot, a fragment of tumor, a mass of muco-pus, or torsion of the renal pedicle. It is also simulated very closely in certain cases of chronic prostatitis and seminal vesiculitis. Hæmaturia is a very variable symptom. In some cases it is more or less continually present, and in others it is never present. In the 21 cases it was present at one time or another in only 8, according to the statement of the patient. It must be remembered, however, that a small amount of blood can only be discovered with the microscope. It is rare to find the urine very red with blood, but sometimes the hæmaturia is so abundant that large clots are passed, often long moulds of the ureter, which are of considerable diagnostic value. Such hemorrhages usually disappear on repose, rest in bed, and cessation from exercise, and are brought on by work, violent exercise, riding in rough vehicles, etc. When infection and inflammation occur secondarily to calculus, and the pus formation is considerable, hæmaturia is less apt to occur, in the writer's experience, and often the attacks of colicky pain disappear. The presence of a swelling noticeable to the patient is rare, and occurred in only 3 of these cases. Gastro-intestinal disturbances are fairly common according to some authors, but were present in only 5 of this series. They consist of a loss of appetite, nausea, vomiting, pain in the region of the stomach, intestinal indigestion, constipation, etc. In some cases they are so marked as to completely obscure the nature of the disease, and in other cases they are very similar to the crises of appendicitis. An enlarged and tender ureter in such cases may render the diagnosis extremely difficult. Digestive disturbances are most apt to indicate a condition of subacute or chronic uræmia

and should lead to a very careful study of the renal function. These are not infrequently associated with headache, ocular disturbances, and other signs of uræmia.

Anuria is one of the most alarming and serious symptoms which occasionally occur with nephrolithiasis. Watson, who has made a careful study of this subject, lays down the underlying causes as follows: (1) The simultaneous blocking of the ureters of both kidneys; (2) the blocking of the ureter of one kidney, the other kidney being functionally incapable; (3) the blocking of the common stem of the two ureters when they are fused, or of the single ureter of a fused kidney; (4) the blocking of the ureter of one kidney and the lessening of the function of the other by reflex influence, the latter organ being normal or but moderately diseased. Calculous anuria is one of the most fatal complications of the disease, as shown by the fact that in 110 cases treated expectantly there were 80 deaths, a mortality of 72 per cent., and in 95 cases treated by operation there were 44 deaths, a mortality of 46 per cent.

Vesical irritability may, according to Watson, Desnos, and others, be the only sign of renal calculus. Watson mentions five cases in which the only subjective symptom was irritability of the bladder. In all of his cases a calculus was passed per urethram. According to Desnos, there is a pain during, and particularly after, urination, with frequent desire and incomplete satisfaction after urination. This, he says, occurs without cystitis, and pressure upon the bladder over the hypogastrium or through the rectum or vagina does not provoke pain. He thinks it is a cystalgia of reflex origin, and that it may become so bad as to be an incontinence.

In the writer's cases vesical symptoms were present in only 6 of the 21 cases, and in very few of these was this more than a slight irritation. Apparently the bladder is usually free from irritation, unless a calculus has passed through the ureter or has become lodged in its lower end, in the juxtavesical, intramural, and intravesical portions of the ureter. In the *Transactions of the American Association of Genito-urinary Surgeons* for 1907 the writer reported 7 cases of calculus lodged in the lower portion of the ureter—2 intravesical, 3 intramural, and 2 juxtavesical—and the following conclusions were drawn: When the stone is situated in the ureter above the bladder the symptoms are pain in the pelvis, sometimes radiating to the penis, but not associated with increased frequency of urination, with pain in the rectum or on ejaculation. Intermittent renal colic occurs, and perhaps pain in the testicle. When the stone is situated in the intramural portion of the ureter and does not project into the cavity of the bladder, there may or may not be frequency of urination; but there is always a pain radiating into the penis at the end of urination, and there is generally pain on ejaculation, either during intercourse or with nocturnal emissions. In one of the three cases there was also pain in the rectum. Intermittent attacks of renal colic also occurred in these cases. When the stone is caught in the ureteral orifice and projects into the bladder the symptoms are more severe than in other locations, and present a remarkable and typical symptom complex of pain, renal, vesical, rectal, seminal, and testicular in character. In one of the cases with this syndrome, the patient complained of a frequent desire to urinate, pain in the bladder, radiating to the glans penis at the end of urination, a constant severe pain in the rectum, which was worse on defecation, a severe pain during sexual intercourse, which came on at the moment of ejaculation, and intermittent attacks of pain in the left kidney and testicle.

Examination showed a calculus about 2 cm. in diameter, projecting partly into the bladder through the ureteral orifice. All of these symptoms disappeared after removal of the calculus. The writer has never seen this combination of symptoms described elsewhere, but the explanation of it is evident as soon as we remember the intimate association of the lower end of the ureter, the seminal vesicles, the rectum, and the bladder.

Diagnosis.—The examination should include a thorough study of the patient, according to modern methods, including careful physical examination, urinalysis, cystoscopy, ureter catheterization, radiography, functional diagnosis of the kidneys, etc. Most of these questions have been dealt with elsewhere. Abdominal examination is unfortunately often very unsatisfactory. In many cases nothing can be made out in the region of either kidney, and in others there is only a slight tenderness. In only 13 of the 21 cases seen by the writer was any abnormality noted in the region of either kidney, and in only a few of the cases was there marked enlargement. Tenderness is supposed to be a very suggestive sign of calculus, but, as stated above, it is very frequently absent. When the kidney is enlarged it is often difficult to differentiate between nephrolithiasis with pyonephrosis and renal tumor. The presence of pus in the urine is more common with calculus, but is also seen in tumor. Careful urinalysis, with estimation of urea, total solids, and the determination of the functional value of the kidneys, with methylene blue and phloridzin, and by the freezing point of the blood, have been very warmly advocated, and before operation is attempted it is important to know the condition of the "other" kidney. Simple cystoscopy will often aid greatly by showing the emission of clear urine from the healthy side, and purulent or hemorrhagic urine from the diseased side; and when the *x*-rays show the presence of a calculus on the affected side, ureter catheterization may sometimes be dispensed with when the operator only wishes to remove the calculus. When nephrectomy is contemplated, it is highly advisable to perform ureter catheterization and to be sure that the "other" kidney is healthy. The radiograph may now be considered, in expert hands, to be a method of great certainty, and almost all renal and ureteral calculi, even of small size, can be demonstrated in this way. The pure uric acid calculus is the most difficult to detect, and some competent radiographers claim that it cannot be shown. Owing to the fact, however, that the pure uric acid calculus is rare, this difficulty does not often arise, and a negative diagnosis at the hands of the best observers can generally be relied upon. Calculi in the bladder, however, are much more difficult to show for various reasons, and a negative diagnosis cannot here be relied upon. The most deceptive shadows are those shown by phleboliths, and as these not infrequently occur in the pelvis adjacent to the lower portions of the ureter, many confusing pictures are frequently shown. The diagnosis is made all the more difficult owing to the fact that these phleboliths are not infrequently associated with pain. In one case the patient had intermittent attacks of severe pain in the region of the bladder, with frequency of urination and pain in the deep urethra, and the *x*-rays showed a shadow which seemed a little far out for the lower portion of the left ureter. Operation demonstrated a phlebolith just external to the left ureter. In such cases a positive diagnosis can usually be made by taking an *x*-ray photograph with a stiletted catheter in the ureter. Fenwick has brought out a special catheter, containing bismuth,

which shows on the *x*-ray plate. As a rule, however, cystoscopy and urinalysis will clear up the diagnosis.

Differential Diagnosis.—The more common diseases which are to be considered are tumor of the kidney or ureter; tuberculosis; essential renal hæmaturia; stricture or torsion of the ureter, with hydronephrosis; vesical disease, such as stone, tuberculosis or tumor; prostatic hypertrophy and carcinoma; chronic prostatitis; seminal vesiculitis. Disease of the spine, such as Pott's disease, bony exostoses, spinal-cord lesions, lumbago, neuralgia, etc., must be considered. We have not space to enter into a full discussion of all these diseases, many of which present certain symptoms in common with those of renal and ureteral calculus. The *x*-rays alone are usually sufficient to make a diagnosis positive, and careful physical, urinary, and cystoscopic examinations are of great diagnostic value. It may be well, however, to lay stress upon the fact that chronic prostatitis and seminal vesiculitis are very frequently associated with pain in the back of a dull, aching character, and localized in the region of one or both kidneys. Not infrequently in these cases crises of pain occur, exactly simulating renal colic, even radiating to the groin and testicle, and not infrequently associated with hæmaturia, irritability of the bladder, frequency of urination, pyuria, etc. The writer has seen more than 10 such cases, in 6 of which an operation had been performed upon the kidney, which was found to be normal. In all of these cases rectal examination showed an extensive chronic inflammatory condition around the prostate and seminal vesicle on the affected side. The hæmaturia and pyuria came from an inflamed posterior urethra, thus making the simulation of renal colic complete. Rectal examination, stripping of the prostate and seminal vesicles, and the microscopic study of the secretion obtained will generally clear up the question at once. In all cases of pyuria, careful search should be made for the tubercle bacillus, as this not infrequently occurs with renal calculus. The differentiation between tumor and stone has been discussed elsewhere. It is often difficult to make a positive diagnosis without the *x*-rays. The cystoscope will generally show if the disease is vesical in character, and careful examination of the spine should always be made as a routine procedure.

Treatment.—When the urine of a patient is known to contain a considerable amount of certain salts, uric acid, oxalates, phosphates, etc., suitable treatment should be adopted to correct this condition. The use of water in abundance, and particularly certain mineral waters, such as those at Saratoga and Poland Springs, Vichy, Contrexeville, Evian, certain German spas, etc., is of value. Healthy exercise, with regular breathing and special diets, according to the salt present, are indicated. The use of urotropin, piperazine, benzoate and carbonate of lithia, etc., have been advised, as these may act as valuable solvents, but it is probable that diet, exercise, and water in abundance are the most valuable methods. When the calculus is formed and is apparently not too large to pass, the use of glycerin in large doses, 50 to 100 cc. daily, has been strongly advised; it is said to provoke painful crises and to be followed by expulsion of the calculus. The writer had success with this in one patient in whom a calculus lodged in the lower portion of the ureter. It is often surprising to find that very large calculi have been passed, and Leonard has taken the position that before operation is carried out every effort should be made to cause the passage of a small calculus. Casper has advised the injection of oil into the ureter, a method used by the writer with success in a few cases.

Dilatation of the ureter below the site of the lodgement of the calculus has also been successful. When the stone is lodged in the very end of the ureter it is sometimes possible to dislodge it with the ureteral catheter, or it may be possible to slit up the ureter by means of an operating cystoscope, and thus facilitate the escape of a calculus. In the female, vaginal massage or stripping from above downward sometimes pushes the calculus into the bladder, and rectal massage has also been advised in the male. Although renal and ureteral calculi may often remain for years without producing severe symptoms, this is not the rule, and usually they lead to very destructive processes in the high urinary tract. Even when the calculus is small its extraction should be undertaken when it has not been evacuated by protracted treatment. It has now been demonstrated that the operation of nephro- or ureterolithotomy is practically free from danger in uncomplicated cases, and that all portions of the ureter are alike amenable to surgical treatment by an extraperitoneal operation, with the exception of the intramural and intravesical incarceration of calculi, in which the intravesical route (surpapubic or cystoscopic) is to be preferred.[1]

When the stone is lodged, and particularly when associated with secondary infection, pyonephrosis, perinephritis, etc., operation should not be delayed. If the kidney is found to be in fairly good condition, nephrectomy usually need not be performed, and it is remarkable that the kidney which is apparently considerably diseased, may often become quite useful and give no trouble after the removal of the calculus. When, however, there is extensive suppuration and the cortex is largely destroyed, the kidney should be removed if the condition of the patient warrants, and if the other kidney is healthy. The use of water in great abundance before and after all operations upon the urinary tract is the first principle. With the imbibition of large amounts of good water, with saline infusions and slowly introduced enemata, uræmia can be prevented even in many cases of severe renal disease, and may be said to be the basis of success both in the medical and surgical treatment of nephrolithiasis. With anuria energetic efforts should be adopted at once to bring on urinary secretion—water in abundance, infusions, enemata, transfusions, sweat baths, hot cups to the kidneys, diuretics, etc. Watson has shown that delay is very dangerous, and if the anuria persists after the use of active medical measures from twenty-four to forty-eight hours, an immediate and rapid operation should be carried out, with the object of incising the kidney and draining the pelvis. If the condition of the patient is dangerous, no attempt should be made to remove the calculus, unless this is very easily accomplished; a secondary lithotomy can be performed later. Casper has advised ureter catheterization and the injection of water or oil into the kidneys, with the idea of dislodging the stone and of stimulating renal secretion. This procedure has been successful, and may be used in appropriate cases; but it is not advisable to wait long before operation is carried out when the condition of anuria persists.

[1] See an article on the subject in the *Annals of Surgery*, May, 1903.

CHAPTER XV.

GENITO-URINARY DIAGNOSIS. DISEASES OF THE PROSTATE.

By HUGH HAMPTON YOUNG, M.D.

EXAMINATION OF URINE.

Methods ordinarily employed in the collection and examination of urine may lead to very grave errors in diagnosis. When all the urine is voided into one receptacle it is impossible to say whether certain pathological constituents may have come from the urethra, prostate, or bladder, but by making use of three receptacles much important data can be obtained at once. In cases of acute gonorrhœa, which is confined to the anterior urethra, if the patient voids urine in only one receptacle it will be cloudy with pus, but if he voids in three receptacles it will be clear in the second and third, due to the fact that the purulent secretions in the anterior urethra have been washed out by the first urine voided. If, however, the inflammation has passed the external sphincter in the triangular ligament and involved the prostatic urethra, the secretion which cannot escape anteriorly through the tightly closed membranous urethra passes upward into the bladder and mixes with the bladder urine. In such cases the urine voided in three glasses shows pus in all three, and cannot, therefore, be differentiated from pus arising from the bladder or kidneys. Blood coming from the anterior or posterior urethra follows the same directions as the purulent secretions described above. In some cases of hæmaturia from the prostatic urethra the bleeding does not occur except at the end of urination, when the final spasm squeezes out the blood from the inflamed or ulcerated verumontanum or middle prostatic lobe. In a similar way purulent secretions which lie in the prostatic ducts in chronic prostatitis often appear as shreds in the last urine voided. Spermatozoa likewise are present in large numbers in the last urine. By the use of the three glass tests a fairly accurate differentiation of the various portions of the urethra is obtained and the origin of many a case of albuminuria, hæmaturia, or pyuria is explained at once. The routine employment of the three-glass test cannot be urged too strongly.

It is important that the urine should be examined soon after voiding, and for this purpose every physician should have a centrifuge, microscope, two or three staining fluids, and the simple apparatus necessary for a fairly complete urinalysis. When the urine is allowed to stand there is a rapid growth of bacteria, and in a short time a precipitate, which often obscures the presence of tube casts or other pathological elements. On this account urinary infections are often completely overlooked. It is particularly important in cases in which instrumentation of the urethra or bladder has been carried out to watch the urine for bacterial infection, and when, in such

cases, the third glass of voided urine shows a cloudiness, it should be examined at once. The passage of urine through the urethra generally washes out all the bacteria which it contains, but if cultures are wanted, or if the diagnosis between the smegma bacillus and the tubercle bacillus is desirable, the anterior urethra should be thoroughly cleansed by irrigation with sterile water, and the penis (particularly the foreskin, glans, and coronal sulcus) cleansed with soap, water, and 1 to 1000 bichloride of mercury solution. If this is done and the urine is voided in three sterile receptacles, the third urine should always be free from extraneous bacterial infection, and if bacteria answering the description of the tubercle bacillus with Gabbett's stain are found, one can be quite positive that tuberculosis is present.[1]

The effect of bacteria upon the secretion of urine and the production of urinary precipitates is very great. Certain bacteria, particularly those of the proteus group, have a very marked alkalinizing effect and cause a rapid deposition of phosphates and the production of calculi. Most ammoniacal urines are due to this bacillus. Some of the staphylococci render the urine alkaline, but they are generally less rapid and intense in their action. Other bacteria, notably those of the colon group, never lessen the acidity of the urine, but in some cases add to its acidity. When bacteria of different effect (alkalinizers and acidifiers) are present they seem to neutralize each other, and with the preponderance of one or the other the reaction of the urine is found to change.

Bacteria are not infrequently present in the urine in large numbers in cases in which there is no pus to be found, and the writer has seen numerous cases of persistent bacteriuria in which no signs of inflammation developed, and only by immediate examination of the urine, voided in three glasses, would the condition have been detected. Such an examination is important in many of the acute febrile conditions, owing to the not infrequent development of bacteriuria and pyuria, and is now well recognized in typhoid fever.

Instrumental Examination.—It may not be amiss to say a few words in regard to the use of the simpler exploratory instruments.

Bougies.—Bougies are of great value in detecting the presence of stricture of the urethra. The best instruments are made of silk or linen covered with gum and provided with an olive-shaped ball at one or both ends, as shown in Fig. 1. The general practitioner should have at least four of these instruments, varying in size from 14 to 26, French scale. They cannot be boiled, and should be cleansed with soap and water and by immersion in 1 to 1000 bichloride of mercury. For stricture of the deep urethra, curved metal sounds are necessary. One should have at least six of these varying in size from 20 to 30 French; they are sterilized by boiling. In their introduction care should be taken, particularly in passing through the membranous urethra, not to produce traumatism, false passage, etc. After the beak has passed into the bladder the instrument may be used as a searcher for calculi. If a No. 28 French passes, the urethra can generally be said to be free from stricture.

Catheters.—There is probably no instrument with which more harm has been done than the catheter, and on this account a word of caution seems advisable. In the great majority of cases in which a catheter is necessary, prostatic hypertrophy is producing the obstruction. In such cases the

[1] For further discussion, see *Johns Hopkins Hospital Reports*, 1906, vol. xiii.

urethra is distorted not only by the pressure of the lateral lobes, but by the upward growth of a median lobe, which usually produces an acute flexure in the floor of the urethra. The size of the ordinary silver catheter or straight catheters of gum or rubber has led to the tunnelling of this median portion of the prostate in thousands of cases, and the pathological museums are filled with many beautiful specimens but sad reminders of medical malpractice. By the use of the coudé (or elbowed) gum-linen catheter, catheterization can be successfully performed without injury in almost all cases of obstruction to urination from prostatic hypertrophy. The acute bend in the instrument, shown in Fig. 2, enables it to ride over the obstructing barrier in the median portion of the prostate. This instrument is indeed the most satisfactory for general use, and should be recognized by the profession as

FIG. 1



Bougie with olive-shaped ends.

the standard catheter to be first employed in nearly all cases. The straight rubber catheter, which is now almost exclusively employed, is often difficult to introduce in normal cases, owing to the fact that its point becomes engaged either in the pouch of the bulb just at the external sphincter, or at the median portion of the prostate, or in front of the external sphincter. The shape of the coudé catheter, on the other hand, enables it to escape being caught in either of these natural depressions. The straight rubber catheter, however, has its place, and is particularly useful in cases of cancer of the prostate, in which it is much more easy to introduce than the coudé catheter. The silver catheter is also of importance, but should usually be employed only when the coudé or the rubber catheter has failed, and great care should be taken to avoid making a false route. In cases of prostatic hypertrophy a special

FIG. 2



Coudé catheter.

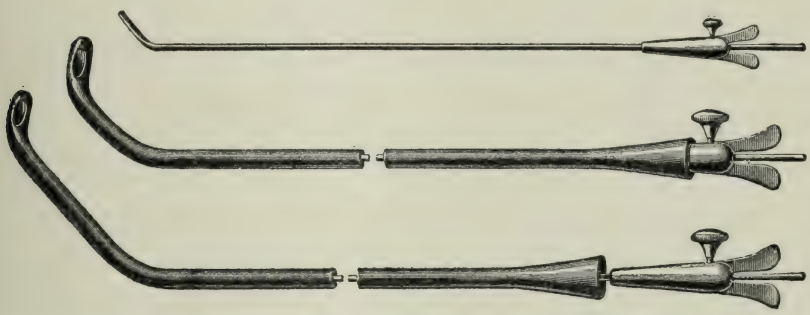
silver catheter with a large "prostatic curve" is often of help, and the two stilets which were invented by Guyon, Fig. 3, enabling one to give almost any curve to gum or rubber catheters, are often of great assistance.

For cases in which retention of urine is caused by a definite stricture, a catheter which can be attached to a filiform is often of great value, the filiform leading the catheter through the strictured portion of the urethra. As it is impossible in some cases to introduce any form of instrument, an aspirating apparatus should always be on hand. The needles which are employed in suprapubic aspiration should not be any larger than the average steel bonnet pin. Aspiration may be repeatedly done with these without much danger and with practically no fear of extravasation.

Asepsis.—Before attempting any urethral instrumentation great care should be taken to prevent infection. The penis should be thoroughly cleansed

with soap and 1 to 1000 bichloride of mercury, and should be surrounded with a sterilized towel saturated with the same solution. The anterior urethra should be irrigated with 1 to 60,000 bichloride of mercury, and the operator's hands cleansed with soap, water, and bichloride of mercury, or other approved methods, before any attempt to introduce the previously sterilized instruments is made. Great care should be taken to avoid traumatism, and the bladder should be irrigated with a solution of 1 to 60,000 bichloride of mercury before the instrument is withdrawn. Usually the patient should take some internal urinary antiseptic (such as urotropin, twenty or thirty grains a day) for several days after the procedure (and if possible before also), and careful examinations of the urine, voided in three glasses, should be made on subsequent days in order to detect the occurrence of infection. If this were done by all practitioners, many of the disastrous results of urethral instrumentation would never occur. It is the rarest thing to find physicians properly equipped with even the instruments absolutely necessary for emergencies, such as they are apt to meet at any

FIG. 3



Guyon's stilet to facilitate introduction of catheter in prostatic hypertrophy.

moment during their professional work, and on this account it seems desirable to give a list of genito-urinary instruments which should be in the possession of every general practitioner.[1] But if the physician is able to invest in only one instrument, let it be a coudé gum catheter, and one that can be thoroughly sterilized by boiling (such as the French make of Porgès).

Visual Exploration.—The use of the urethroscope and cystoscope has become so greatly popularized of late that a few words may not be amiss. Here, too, great care should be taken to avoid infection, and on this account the urethroscope of Otis, in which the light is not carried in the tube of the instrument, but is thrown in from without, is much to be preferred. By its use diagnosis of obscure urinary lesions can occasionally be made. The topical treatment of chronic gonorrhœa and diseases of the verumontanum

[1] Glass urethral nozzles for antiseptic irrigation of the urethra and bladder. Sounds for dilatation of the urethra (Nos. 18, 20, 22, 24, 26, 28, French). Filiforms, for strictures of small calibre, with screws for attachment to dilating followers (Nos. 10, 14, 18, 22, French). Catheters: Coudé prostatic gum silk catheters which can be boiled (Porgès) (Nos. 14, 16, 18, French). Rubber straight "Nélaton" catheters (Nos. 10, 14, 16, 18, French). A silver Van Buren curve (No. 16, French). Guyon's stilets, coudé and Béniqué curves (to give a proper curve to gum and rubber catheters).

is often of very great benefit. Cystoscopy may now be divided into two types, that performed with the bladder distended with water, and that performed with the bladder distended with air.

It is impossible here to discuss the advantages and shortcomings of both these methods, but suffice it to say that for general diagnostic work, thorough inspection of the entire bladder, study of the action of the two ureters and of the size and distribution of the prostatic lobes, the simple cystoscope of Nitze with the bladder distended with water is by far the best instrument. This little instrument, with its coudé beak, is one of the easiest to introduce, and with the use of cocaine in the urethra its employment is rendered extremely simple and free from pain. Its findings are usually so certain, and often so brilliant, that it seems remarkable that it is not now used with far greater frequency. With the simple cystoscope it is possible not only to distinguish between the various diseases of the prostate and bladder, but also by simple study of the ureteral orifices it is possible to give an accurate interpretation of the condition of the two kidneys in many cases.

Renal hæmaturia or pyuria can easily be detected by simply watching the intermittent outflow of urine from the ureteral orifices, and in most cases of unilateral renal disease a pathological condition of the lower end of the ureter can generally be detected. In many cases ureter catheterization is not at all necessary.

For intravesical treatment the use of an open tubular cystoscope and vesical distention with air is generally to be preferred, and in the female this method has been very successfully used by H. A. Kelly. In the male, catheterization of the ureters can be done by both methods, and, as a rule, with great ease. It is no longer a very difficult procedure, and can usually be accomplished with very little pain after the use of cocaine in the urethra. The writer's preference is for the catheterizing cystoscope of Nitze, made by Leiter in Vienna, which is provided with two catheters, and at the same time is of very small size, so that its introduction is not difficult. Ureteral catheterization has not become so easy that it is to be recommended as a routine procedure by all practitioners. It can be learned, however, without great difficulty, and it should be employed much more widely than it is. By the use of formalin vapors, thorough sterilization of the ureter cystoscope and catheters can be obtained without much difficulty, and the dangers of vesical and ureteral infection can be reduced to almost nil. The development of these remarkable optical instruments has been one of the greatest additions to medicine, and has changed a great field of diagnosis from one of guesswork to one of the most certain. Hidden organs have been brought from darkness to visual inspection, and as a result some of the most brilliant advances in surgery have been made.

THE DIAGNOSIS OF CERTAIN GENITO-URINARY AFFECTIONS.

Urethritis.—The characteristics of the gonococcus are so well known to-day that it would hardly seem necessary to say anything in regard to the microscopic diagnosis; but although everyone knows that the organism appears usually as a diplococcus of biscuit shape, intracellular, and that it decolorizes by Gram, very little is generally known about the so-called pseudo-gonococci and the persistence of gonorrhœa without gonococci.

In an acute urethritis with a profuse discharge of pus the gonococcus is usually found so quickly and in such great numbers that a positive diagnosis is easy. When, however, the discharge is slight, or the only purulent secretion present is found in the shape of shreds in the urine, the detection of the gonococcus is often very difficult. This is due first to the presence of other organisms which closely simulate the gonococcus. Some of these do not decolorize by Gram, although they are typical in shape and intracellular; but there are others in which the organism is not only a biscuit-shaped diplococcus, but also decolorizes by Gram. Fortunately, the latter organism is found very rarely in the urethra (according to See, in a proportion of 2 per cent. of the bacteria found in the normal urethra). These pseudo-gonococci are non-pathogenic and have never been found except in very small numbers, so that if the rule is made to make a positive diagnosis of the gonococcus only when present in fair number, and when located within the pus cells, no mistake will be made, according to See. But the absence of the gonococcus after a careful microscopic examination is not sufficient to warrant the assertion that the case is non-infectious and harmless to the opposite sex. In the majority of cases of chronic gonorrhœa it is almost impossible to find the gonococcus or in fact any organism, but multitudes of cases of pelvic inflammatory trouble in women prove the fallacy of the idea that these patients cannot transmit infection. Examinations made at operation on pelvic diseases in women show in a great many cases no evidence of bacteria, thus demonstrating apparently that it is not necessary to have the gonococcus present in order to transmit an acute or chronic venereal disease.

The absence of the gonococcus is not the all-important question. Of course, whenever the gonococcus is present the condition is far from cured, but because it cannot be found or even because there is no evidence of a urethral discharge is no justification for the habit of telling the patient that he is cured. Before a gonorrhœal patient is discharged as well, he should undergo a careful routine examination, which should include examination for discharge at the meatus, and shreds in the urine, voided in three glasses; palpation of the prostate and seminal vesicles; expression of their contents for microscopic study and the examination of the urethra with a sound for infiltrations, strictures, etc. As long as urethral shreds composed largely of pus cells are present the patient cannot be considered well. As long as the prostate is enlarged, indurated, and the secretion contains pus cells in considerable number there is great danger to the opposite sex. The fact that a marked prostatitis may be present, when there is no evidence of chronic urethritis at the meatus or in the urine, shows the very great importance of a routine examination of the prostate and seminal vesicles, and even when the prostate feels normal it is important to examine its secretion, which can easily be made to appear at the meatus simply by vigorous massage. The normal secretion is largely composed of lecithin cells, which are easily recognized, and the presence of a definite number of polynuclear leukocytes, as shown by the addition of acetic acid, demonstrates at once the presence of a chronic inflammatory condition of the prostate. Fortunately, this condition is generally curable by a prolonged course of prostatic massage and other local treatment, but until such cure is effected, marriage is generally a hazardous procedure, even if repeated careful examinations fail to show the presence of the gonococcus.

Chronic Prostatitis.—The importance of chronic prostatitis, which is one of the most common diseases with which the adult male is afflicted, and the fact that it is responsible for symptoms in regions far remote and simulates many other affections, are very little appreciated. The symptoms of chronic prostatitis may be sexual, urinary, or referred. Only the last is discussed here, as we have not space to refer to the numerous sexual disorders or to the urinary irritations and obstructions produced by chronic prostatitis. The referred symptoms are of a painful nature, and may involve the back, hips, thigh, rectum, perineum, groins, and scrotum. They seem to occur in four distinct groups: (1) Those involving the rectum, perineum, and urethra; (2) those involving the groin and scrotum; (3) those following the course of the sciatic nerves and involving the legs, thighs, hips, and buttocks; and (4) those involving the back and region of the kidneys.

These referred pains are generally of a dull, aching character, coming on at certain periods of the day; in some cases painful seizures of considerable intensity occur. This is particularly true of those cases which simulate renal colic, often being of such severity as to require morphine. They are often accompanied by hæmaturia and marked irritability of the bladder (both due to an inflamed prostate), and the simulation of the symptomatology of renal calculus is often perfect. Rectal examination in these cases usually shows a marked inflammatory infiltration, involving the prostate, seminal vesicle, and surrounding structures in the pelvis on the side in which the pain occurs. The explanation of these referred pains is, according to Head, that a painful stimulus received at an internal organ is directed upward to that segment of the cord from which its sensory fibers are given off; there it comes in close communication with the fibers from the surface of the body which arise from the same segment, and thus, by a psychic error, the pain is referred to another region than that of the viscera actually affected. The prostate receives fibers from the tenth, eleventh, and twelfth dorsal, the first, second, and third sacral, and the fifth lumbar segment. With this varied distribution it is easy to see how the referred pains occurring as a result of chronic prostatitis may simulate, as they do, lumbago, nephrolithiasis, coxalgia, sciatica, rheumatism, varicocele, and other conditions in the various regions from the diaphragm to the toes. It is safe to say that chronic prostatitis is responsible for many of the so-called neurasthenias in the male, and that many painful maladies which go untreated could easily be recognized if careful examination was made of the prostate and its secretion.[1]

It is very important for practitioners to make a routine examination of the prostate as a regular part of physical examination in order that they may become adept in recognizing slight changes in the gland and its adnexa. With the patient bending forward with his elbows upon his knees, the index finger (covered with a rubber cot) is inserted into the rectum, and systematic examination of the membranous urethra, prostate, seminal vesicles, and vasa deferentia made. With practice, no difficulty is usually experienced in mapping out these structures and in determining pathological changes. In chronic prostatitis the prostate is often somewhat enlarged, irregular, sometimes nodular, with induration in places, and at times great tenderness.

[1] Those who are interested will find an extensive report of cases in the *Johns Hopkins Hospital Reports*, 1906, vol. xiii.

It is apt to be associated with an induration along the vasa deferentia and lower portion of the seminal vesicles, and continuous with that of the prostate. In some cases the entire seminal vesicle is enlarged and indurated, and the space between the seminal vesicle may be filled up by a broad plateau of infiltration which connects the indurated vesicles. Adhesions to the pelvic wall on one or both sides, fixing the prostate and sometimes the seminal vesicles, is a fairly common finding, the periprostatic infiltration occasionally being very extensive. In some cases the prostate appears normal; it is impossible to make out any enlargement, irregularity, or induration, and the great importance of obtaining some of the secretion by massage or stripping of the seminal vesicles or prostate is evident. This stripping process, carried on systematically from above downward, soon empties considerable secretion into the prostatic urethra, from which it may be carried, by a similar stripping movement, through the external sphincter, after which it runs down freely to the meatus, where it may be caught upon a slide for microscopic examination. In normal cases the prostatic secretion is composed largely of lecithin cells, which are small, translucent, non-nucleated bodies, varying in size from that of a blood platelet to that of a red blood corpuscle. Large granular cells, epithelial cells, and spermatozoa are also seen. If trauma has been produced, red and white corpuscles may be present. By the addition of acetic acid the presence of leukocytes is demonstrated at once. Often by the microscopic examination alone the presence of a chronic prostatitis is recognized. The writer strongly urges the necessity of this examination as a routine procedure.

Chronic prostatitis is essentially a peri-acinous infiltration. The accompanying processes in the seminal vesicles and in the periprostatic and perivesical tissues are much the same. In these processes the nerve terminals, fibers, and ganglia are frequently involved, and to this is due the many referred pains which occur. The purely sexual symptoms are most often due to changes in the verumontanum, characterized by infiltration, enlargement, congestion, and dilatation of the ejaculatory ducts. The urine in these cases is apt to show fine comma shreds in the third urine voided, due to the squeezing out of purulent plugs or moulds from the lumina of the prostatic ducts during the last spasmodic efforts of urination. Spermatorrhœa may be present also.

In a study of 358 cases of chronic prostatitis the symptoms were as follows: Frequency of urination, 90 cases; pain during urination, 46; urgency of urination, 25; difficulty of urination, 11; irritability of the deep urethra, 11; pain at the end of urination, 7; pain at the beginning of urination, 3; and dribbling after urination, 1. In 34 cases definite obstruction to urination was present, but in only two cases was the retention of urine complete. These men were thirty-two and thirty-seven years of age, and one had led a catheter life for twelve years. (These patients were cured by perineal prostatectomy.) The location of the referred pains was as follows: Lumbar region, 64; region of the kidney, 8; of a colicky nature simulating renal colic, 10; in the perineum, 35; suprapubic, 22; groin, 18; urethra, 14; rectum, 13; thighs, 12; hips, 10; sacrum, 5; simulating sciatica, 5; knees, 4; and legs, 4.

In some cases these painful seizures were of great intensity. This is particularly true of those cases which simulated renal colic, the attacks being of such great severity as to require morphine. These attacks are not infrequently accompanied by hæmaturia and marked irritability of the

bladder (both due to posterior urethral inflammation), so that the simulation of renal colic due to calculus is often perfect, and in six of the ten cases exploratory operation had been performed on the kidney without finding a calculus. Rectal examination in these cases usually showed a marked prostatitis, with infiltration around the seminal vesicles and adhesions to the pelvic wall. The treatment of these cases is most satisfactory, and consists in prostatic massage, very hot rectal douches given with Martin's rectal tube, local application of nitrate of silver to the verumontanum and posterior urethra, intravesical irrigations, dilatations, etc. Frequently extensive infiltration of very chronic character and involving apparently the whole floor of the pelvis disappears under this treatment, with an immediate amelioration and the final cure of symptoms of long duration. Before a diagnosis of neurasthenia in the male is made a most careful examination of the prostate and seminal vesicles and their secretion should be made.

Tuberculosis of the Genito-urinary Tract.—With an insidious hæmaturia or pyuria the suspicion of the presence of tuberculosis in some portion of the urinary tract generally arises. Owing to the fact that tuberculosis is very rarely primary in the bladder, it is important to recognize the original focus of the infection. Although the bladder is infected in the majority of cases, the primary site is generally in the kidney, the prostate and seminal vesicles, or the epididymis, and in many cases all of these structures ultimately become involved. In cases of tuberculosis of the epididymis, prostate, and seminal vesicles, palpation will generally make the diagnosis clear at once; but in some cases the differentiation between tuberculosis and a chronic inflammatory condition is not easy, and it is important to find the bacilli. As remarked above, if care be taken to cleanse the penis, irrigate the anterior urethra, and collect the urine in three sterile glasses, one can be positive that an organism obtained from the third urine which answers the proper staining tests is the tubercle and not the smegma bacillus. In many cases it is advisable to determine the extent of vesical involvement and the presence of tuberculosis of either kidney, and for such the cystoscope is very necessary. Fortunately, by ureteral meatoscopy (a term invented by Fenwick to designate a simple inspection of the ureteral orifices) it is possible to form a very accurate idea of the condition of the kidneys on that side. If tuberculosis is present the fluid ejected will be cloudy, and perhaps show a large amount of muco-pus, and the mucous membrane surrounding the orifice will usually show marked inflammatory changes, varying from hyperæmia and œdematous swelling to severe ulceration. In many cases it is not necessary to perform ureteral catheterization, but when it is advisable this can usually be carried out without much difficulty (unless the bladder be too irritable or contracted) by the simple use of an instillation of cocaine.

Before the performance of nephrectomy one should be absolutely certain that the other kidney is functionating, and if there is any doubt as to the soundness of the unsuspected side, ureter catheterization should be carried out. It is needless to say at this date that the various segregators are absolutely unreliable, especially in cases of tuberculosis. It may not be amiss to remark that while surgical treatment of tuberculosis of the prostate and seminal vesicles has been a disastrous failure, it has been more than atoned for by the brilliant results of nephrectomy and epididymectomy and the

fact that after removal of these foci of infection fairly extensive tuberculosis of the bladder and prostate has been found to disappear in many cases.

Hypertrophy of the Prostate.—According to Sir Henry Thompson, one man in every five over fifty years of age suffers from prostatic hypertrophy. Many of these cases never cause much trouble, but the great frequency of the disease, and the fact that it is first seen by medical men, warrant a few words upon the subject.

Prostatic hypertrophy usually consists of many spheroids of hypertrophic gland tissue bound together in a fibrous stroma, the whole forming an encapsulated lobular mass, which presses against the urethra and may extend far into the bladder. In 120 specimens examined by us, 100 were of the glandular type, 14 of the fibromuscular, and 6 inflammatory. Besides the enlargements of the lateral lobes, a more or less considerable hypertrophy of the median portion of the prostate, the so-called middle lobe, which lies beneath the urethral orifice at the vesical opening, is very commonly present. This produces by its growth a bar at the neck of the bladder, which acts not only as an obstruction to the outflow of urine, but to the introduction of a catheter. In nearly all such cases there is an acute bend in the urethra, sometimes with a formation of a pouch in front of this median bar or lobe. This is also often associated with a contracted condition of the prostatic orifice, so that the introduction of a straight instrument is in many cases impossible.

The usual results of prostatic obstruction are at first frequency of urination and a gradual contracture of the bladder, with progressive lessening of its capacity. Later, the bladder is not completely emptied, and the amount of residual urine gradually increases. Complete retention of urine sets in, as a rule, without warning, and, in some cases, when there has been very little difficulty of urination. Often the passage of a catheter will be followed by a complete retention of urine, which may not disappear until operation is performed. The bladder usually becomes trabeculated, and pouches and diverticula form, in some cases reaching great size. Dilatation of the ureters and renal pelves is often present to a marked degree when the symptoms do not suggest any such changes, and if an ascending infection occurs the case at once assumes a desperate character. The symptoms are usually those due to gradually increasing obstruction, viz., hesitation, straining, increased frequency of urination, with smallness of the stream, and often several isolated attempts or efforts are required before the act of urination is completed. With increase in the residual urine, urination gradually becomes more frequent and difficult, and in most cases complete retention, and a catheter life ultimately results. In rare instances the bladder may become very greatly distended, and although the residual urine may be great (from 1000 to 2000 cc.), the overdistended bladder is able to functionate apparently quite normally, voiding large amounts of urine at long intervals, so that one is surprised to find a greatly distended bladder, with a large amount of residual urine. In other cases incontinence, generally with considerable residual urine, is present. The varied symptomatology cannot be discussed in detail, but we wish to lay stress upon the fact that often with few symptoms present very serious destructive processes are going on, and, almost without warning, the patient is often found to be in a desperate condition. The great importance of instituting treatment early, before the occurrence of a large amount of residual urine and before the formation

of diverticula and hydronephrosis, is shown by the fact that in early cases operation is practically free from danger, whereas in the latter class of cases there is always danger of uræmia, although it is possible with careful treatment to help nearly all of these patients.

As remarked above, a special "coudé" catheter should be employed in cases of prostatic hypertrophy, because the abrupt curve near the point of the instrument enables it to ride up over the median bar. The use of straight rubber catheters, and even the ordinary silver catheter, is, as a rule, dangerous, and the straight olive-tip pointed silk catheter should never be used.

The question as to what is the proper treatment to follow when the patient comes into the hands of the practitioner is of great importance. It is well recognized that a large amount of residual urine should never be allowed to continue indefinitely, owing to the injurious effect upon the higher urinary organs, and on this account many have advised systematic catheterization when the amount of residual urine is larger than 150 cc. Unfortunately, the first catheterization is not infrequently followed by complete retention of urine, necessitating the beginning of a catheter life, and on this account, when one considers catheterizing for the first time, he must always be prepared for such a result. It is not safe to withdraw residual urine and leave the patient thinking that he will be able to void as before; and as frequent catheterization is almost always followed by infection of the bladder, cystitis, etc., the question of the employment of the catheter is a serious one. Carefully compiled statistics of Casper and of Rovsing show that the catheter life is a very dangerous one, with a very considerable mortality. The use of a catheter, even in the hands of skilful patients, with abundant means at hand to perform it properly, is frequently beset with great difficulties and serious complications, such as false passages, catheter fever, prostatic abscess, unrelieved retentions, with increased dilatation of the ureters and kidneys, ascending infection, etc. The breakdown of catheter life occurs in a large percentage of the cases before many months have passed, and a surgical operation is then often required in an emergency to save life. On the other hand, the surgical treatment of prostatic hypertrophy has progressed rapidly in the past decade, and the operation of prostatectomy has now become remarkably simple and free from danger, even though the surgeon is still required to treat many patients who have suffered from the disease for a long time and are in serious condition on account of numerous complications. The operative mortality of perineal prostatectomy varies from 3 to 6 per cent. in the various statistics, and of suprapubic prostatectomy from 6 to 10 per cent.

Owing to the terrible suffering of some of these unfortunate patients, operators have been induced to do the operation upon desperately ill and very aged men, and this fact is largely responsible for the presence of any mortality. For example, the writer has had 12 deaths following 350 cases of perineal prostatectomy. About 30 per cent. of these patients were over seventy years of age and 12 over eighty years of age, and among the 12 deaths, 5 were over eighty years of age. One of these patients, eighty-seven years of age, died four weeks after the operation, of pneumonia, and one, aged eighty-nine, eight weeks after the operation, from epistaxis.

To show that the operation is extremely benign, the writer had (from July 24, 1905, to March 20, 1908) 128 consecutive cases of perineal pros-

tatectomy without a death, every patient leaving the hospital well or improved. Four of these patients were over eighty years of age, 19 between seventy-five and seventy-nine, and 22 between seventy and seventy-four. Many of these patients, besides being very aged, were in poor physical condition. In 20 cases more or less severe organic heart disease was present (dilatation, endocarditis, myocarditis, and arteriosclerosis). In 5 cases emphysema of the lungs and in one case double pulmonary tuberculosis was present. In 6 cases pyelitis or pyonephrosis, in one case renal calculi, and in another ureteral calculi were present. These statistics are mentioned to show that there was no choosing of the cases, and that the operation of conservative perineal prostatectomy is a satisfactory one.

It seems evident, therefore, that all patients with prostatic hypertrophy and gradual increasing obstructive symptoms should be subjected to operation before serious complications arise. The use of a catheter even for a protracted period is not to be advised, as it almost invariably results in infection, which is often very difficult to remove. When, however, the amount of residual urine is large, say 400 to 2000 cc., frequent catheterization should be carried out for a protracted period before operation, so as to allow the distention of the ureters and kidneys to be relieved. In some cases it may be advisable to fasten a retained catheter in the urethra, and it is remarkable how such drainage leads to a rapid improvement of the function of the kidneys. In numerous instances severe uræmia has cleared under this treatment (water in large amounts by mouth, by rectum, or by infusion being given at the same time). In such cases rapid improvement in the urine is noted, and, as a rule, operation should not be undertaken until this improvement has been sufficiently marked to indicate that there is very little danger of renal suppression after operation. When catheterization is necessary the patient should be instructed to do it with proper antiseptic precautions, and he should be provided with coudé silk-gum catheters of various sizes. All such patients should take urotropin (from 15 to 40 grains daily (gm. 1 to 2.6), to prevent urinary infection. The medical man, however, is not justified in allowing his patient to adopt a catheter life unless the patient refuses operative treatment, which all statistics show to be not only the least dangerous but also brilliant in its results.

Cancer of the Prostate.—Recent statistics have shown that this disease is far more common than previously supposed. In five years in the writer's private practice there were about 250 cases of benign prostatic hypertrophy and 68 cases of carcinoma of the prostate—the proportion between cancer and hypertrophy was therefore 1 to 4. The rectal findings in carcinoma are usually so different from those of hypertrophy that there is no difficulty in diagnosis. In most cases cancer is not associated with hypertrophy of the prostate. The prostate is often much larger than normal, but it does not, as a rule, have any of the large rounded adenomatous lobes found in hypertrophy, and there is usually no intravesical outgrowth of lateral or median lobes. The cancer begins most often beneath the urethra, and from there grows along the ejaculatory ducts, finally involving the space between the seminal vesicles beneath the trigone, from which it may in some cases invade the bladder. Slight elevation of the median portion of the prostate is not infrequently present, but rarely in the shape of a rounded intravesical lobe, as remarked above. In a few instances adenomatous hypertrophy of the lateral lobes, which may project into the bladder, is present, with a layer of

carcinoma behind it, and just beneath the capsule of the prostate. The so-called malignant degeneration in previously benign prostates occurs very seldom in the writer's opinion, and one should almost always be able to recognize carcinoma either by examination or at operation before the prostate has been removed.

The *symptoms* of cancer of the prostate are unfortunately very similar to those of hypertrophy. In a study of 87 cases seen by the writer, 50 per cent. occurred during the seventh decade, and only one case before the age of fifty. The first symptoms were usually frequency of urination, sometimes associated with difficulty and occasionally burning in the urethra. In 13 cases the first symptom was pain, located in the penis in 5, in the bladder in 4, in the thigh in 4, in the testicle and groin in 3, in the hip in 3, in the pubes twice, rectum once, legs once, and back twice. The pain was usually slight, but in some cases severe, and in some the diagnosis of rheumatism, neuralgia, sciatica, and lumbago had been made. Hæmaturia was the symptom at onset in only 4 cases. In one case the only symptom was swelling of one leg. The frequency and difficulty of urination are similar to that seen in prostatic hypertrophy. Retention of urine with a catheter life not infrequently comes on. Hæmaturia is no more marked than in hypertrophy, but, as a rule, pain is a much more prominent symptom, especially in the later stages of the disease. In the writer's patients most of the regions beneath the diaphragm were the seat of neuralgias.

The *diagnosis* of carcinoma of the prostate is easy in the later stages, when the large stony mass of induration, involving the prostate, seminal vesicles, and intravesicular region, is present. When, however, the disease is still confined to the limits of the prostatic capsule, diagnosis is much more difficult. Examination of the writer's patients showed that cancer was almost always associated with a stony induration of part or all of the prostate. On cystoscopic examination there were generally no intravesical lobes, as usually seen in hypertrophy, and when the suburethral portion of the prostate was examined with the finger, while the cystoscope was still in the urethra, it was almost invariably found to be more thickened and indurated in carcinoma than in hypertrophy. A markedly indurated prostate in a man over fifty years of age should always be viewed with suspicion and, unless carcinoma can be excluded, should be subjected to an early exploratory prostatectomy. When the posterior surface of the prostate is exposed through the perineum it is usually possible, by palpation and inspection, to recognize carcinoma. In some cases, however, it has been necessary to make an incision into the prostatic lobes and excise a piece of tissue for frozen sections and microscopic examination. This procedure can be carried out in ten minutes, and if the disease is benign the ordinary enucleating prostatectomy can be carried out; but if malignant and no high infiltration is to be felt, a radical excision should be adopted.

A study of the pathology showed that in order to obtain radical cures it would be necessary to excise not only the prostate with its capsule and urethra, but also the seminal vesicles and anterior portion of the vesical trigone (the defect closed by anastomosing the bladder with the membranous urethra). This operation the writer carried out in five patients, and one is now apparently entirely well four years after the operation. The treatment of advanced cases of cancer of the prostate may be divided into three classes:

1. Those in which urination is not extremely frequent or painful. Here a let-alone policy is usually advisable. The patient should be told not to let the bladder become overdistended.

2. Those in which urination is frequent and the amount of residual urine is large. In such cases the use of a catheter often gives great relief, and removes the danger of renal complications from back pressure. A straight rubber "Nélaton" catheter (the ordinary red rubber catheter) is usually the best to employ, and several sizes should be on hand; but the largest that can be comfortably passed should be used so as to keep the posterior urethra somewhat dilated. In most cases the coudé prostatic gum catheter does not pass easily—the beak catches in the prostatic urethra, which is usually strictured and not merely compressed, as in hypertrophy. A silver catheter should be employed only when others fail, and then with great care. The catheter life may be followed for a long time with success if cleanliness is observed, and if the patient takes urotropin off and on to avoid cystitis.

3. Those in which catheterization is difficult or painful. In these cases operative relief is generally necessary, and suprapubic drainage is usually employed. This necessitates the wearing of some form of apparatus, such as the Bloodgood bag. In some cases the patient gets along fairly well.

The Bottini electro-cautery operation may be used, and in some cases the results have been brilliant and permanent, the patient being able to void urine with fair comfort until the end.

A conservative partial perineal prostatectomy may also be done, the object being to remove the obstructive pressure of the lateral and median portions of the prostate. The writer has employed this operation in more than a dozen cases, with excellent results. One patient lived three years, and had no return of the obstruction to urination.

PART II.

DISEASES OF THE DUCTLESS GLANDS.

CHAPTER XVI.

DISEASES OF THE ADRENAL GLANDS.

By GEORGE DOCK, M.D.

The adrenal glands, discovered by Eustachius in 1564, did not acquire importance until Addison's work (1854) on the disease that now bears his name. The topography and gross anatomy of the glands need no detailed description, but some general data and a note of some recent additions to our knowledge are necessary before taking up the consideration of adrenal disease. The adrenals are composed of two parts, as shown by Kölliker, the cortex and medulla. The cortex measures from 0.28 to 1.12 mm. in thickness; the medulla, 0.35 to 0.75 mm. in the periphery, from 2 to 3.3 mm. in the inner part. The glands are smaller in advanced age. Negroes are said to have larger ones than Caucasians. The weight of the glands varies from 4.8 to 7.3 grams, depending partly on the amount of blood.

The blood supply is large and is noteworthy from the fact that the same blood circulates through both cortex and medulla, and partly in a cavernous system, so that it is separated from the cells of the gland, in many places, only by an endothelial layer. According to Manasse and others, even this layer is absent in some places. The lymphatics are numerous.

Many nerves enter the adrenals, thirty-three on the right side, according to Kölliker, medullated and non-medullated. They are derived from the semilunar ganglion, renal plexus, splanchnic, and vagus. Their branches pass between the cylinders of cortical cells and ramify closely among the cells of the medulla.

Development.—The cortex of the adrenals develops in the "inter-renal zone" of the cœlom-epithelium (Wolffian body). Remains of the inter-renal buds give rise to accessory adrenals, including those of Marchand.

The Chromaffin Tissue.—The medulla develops from the anlage of the sympathetic ganglia. Until recently it was looked upon as either nervous or of cortical origin, but the investigations of A. Kohn[1] (1898 and later),

[1] Of Kohn's numerous articles, it is enough to refer to the following, where other references may be found: "Das chromaffine Gewebe." *Ergebnisse der Anat. und Entwickelungsgeschichte* (Merkel-Bonnet), Band xii. 1902–1903; "Die Paraganglien." *Archiv f. mik. Anat.*, Band lxii. See also Wiesel, "The Anatomy, Physiology, and Pathology of the Chromaffin System, etc.," *International Clinics*, 1905, vol. ii, 15th series, p. 288.

Wiesel, Biedl, and others put the sympathetic origin beyond doubt. From the researches made by and stimulated by Kohn, it appears that the medulla of the adrenals is the most extensive collection of "chromaffin tissue," a cellular material rich in vessels and nerves, and including as its most important constituents the "chromaffin cells." The cells are characterized by their intense yellow or brown reaction with chromic salts (Henle, 1841; Stilling, 1890). Stilling's term "chromophile" tends to error, as it is used also in connection with reactions to dyes; Poll's more accurate name, "phæochrome" (φαιός, brown) does not seem likely to be adopted. "The chromaffin tissue has the same histological arrangement in different parts of the same individual and in different classes of vertebrates. It presents a characteristic cell type in all vertebrates so far examined. It has in all organs and in various animals the same histogenesis—the sympathetic. Its extracts, so far as they have been examined, have the same physiological action."[1] Small or large groups of such cells are found on the sympathetic nerves, "from the neck to the coccyx," in the ganglia, and on and in the great vessels. To independent groups of the tissue Kohn gives the name of "chromaffin bodies" or "paraganglia." These appear as roundish or elongated bodies, with connective tissue capsules, and provided with nerves, and very richly with bloodvessels. The medulla of the adrenals is the largest collection of such tissue. Others are the carotid and (probably) the coccygeal glands and "Zuckerkandl's organ." Wiesel also describes the same tissue in the hypophysis. Much of the chromaffin tissue undergoes atrophy in fetal life, but Wiesel found chromaffin cells in the sympathetic of old people. Aschoff and Kohn think that many so-called "accessory adrenals" have really been chromaffin tissue.

Accessory adrenals, made up of cortical tissue and resembling the zona fasciculata of the cortex in structure, are of frequent occurrence, being found in almost all bodies examined (less frequently in advanced age), from the liver to the genital organs. Their number varies in different animals. Rats have them in most instances, guinea-pigs less frequently. True accessory adrenals, containing cortex and medulla, are rare, but sometimes occur in the solar plexus, less frequently in other parts. In some cases in which medullary tissue has been claimed to occur, as in certain adrenals of Marchand, Aschoff thinks postmortem changes had led to error. Wiesel would limit the name accessory adrenals to bodies of cortical structure, and looks upon the others as "chromaffin bodies."

The importance of such a system of tissue in pathology is obvious, and the necessity of taking it into consideration in suspected cases of adrenal disease is imperative.

Physiology.—Notwithstanding an immense amount of investigation, from the time of Brown-Séquard's experimental work in 1856, our knowledge of the functions of the adrenals is still very incomplete.

The extract of the adrenals stimulates vessels and muscles, as shown by Oliver and Schaefer, Szymonowicz and Cybulski, Langlois, Boruttau, Biedl, Blum, and others, causing a rise of blood pressure so marked that with large doses the mercury may be forced out of the manometer. The action is partly peripheral, on the arterioles, but the Meltzers have shown

[1] Gierke, "Chromaffines System und seine Pathologie," *Ergebnisse der allg. Path.*, 1904–1905, Jahrg. x, p. 502 et seq.

that suprarenal extract stimulates both vasoconstrictors and vasodilators, and Oliver and Schaefer, Gottlieb and Boruttau have shown a direct action on the heart itself. Part of the rise of pressure is due to increased heart action (Velich). Sometimes the auricles cease beating, the ventricles keeping up the circulation. The cardiac inhibition is due to stimulation of the medulla. The pulse becomes slower, the respiration shallow and infrequent. The effect upon skeletal muscles lasts longer than that upon the bloodvessels, and Schaefer thinks the active principle is taken up and stored by the muscles. It is also not excreted by the urine, nor at once re-absorbed by the capsules. "Its ultimate disappearance is probably due to a process of oxidation occurring within the tissues" (Schaefer[1]). Miller, however, found that adrenin was taken up by the blood, so that the blood of a rabbit to which it has been administered, but no longer shows the effect, will cause a rise of blood pressure if injected into another rabbit. Among the most striking effects of adrenal extract is glycosuria, which can be produced by the hypodermic or intravenous injection of the extract. The glycosuria is prompt but transitory, but can be kept up by repeated injections.

That the adrenal cortex does not produce this substance is proved by several facts. Fresh cortex of the horse has no such action, but after a few hours, when diffusion has had time to take place, it has a slight effect. In selachians, with separate cortex and medulla, the cortical (inter-renal) part has no action, the chromaffin (suprarenal) part has the usual effect (S. Vincent, Biedl, Wiesel). Biedl and Wiesel, and Mulon, produced glycosuria with extracts of the organ of Zuckerkandl and carotid gland (horse) respectively. Biedl got the effect from chromaffin tumors, but not from Grawitz's (cortical) tumors. Zanfrognini got a blood pressure raising effect from an adenoma of the medulla. The ferric chloride and chromic acid reactions, and the effect upon the walls of arteries, investigated by K. Ziegler[2] and others are all due to the chromaffin medullary extract.

The extract from all animals has the same action. It is soluble in water, insoluble in alcohol, dialyzable, not destroyed by acids or gastric juice. Its active principle is not yet known with certainty. The adrenalin of Takamine represents it more perfectly than the epinephrin of Abel and the suprarenin of Fuerth (Aldrich), but probably all are mixtures (Moore and Purinton). Other names for the substance are sphygmogenin (Fraenkel) and hemisine. Schaefer proposes the name adrenin. A synthetic adrenin has been made by Stoltz (1907), but according to Cushny it is inferior in action to the natural preparation.

As might be expected from the histogenesis of the medulla, the adrenal of the fetus does not contain the medullary extract (Svehla,[3] Moore and Purinton).[4] From the facts referred to, it is certain there is an important relation of all parts of the chromaffin system to each other. It may be said to compose the "hypertensive system," with the power of vicarious action and compensation.

It is certain that the cortex has a wholly different function from the medulla, but the details are not known. It seems probable there is an internal secretion, with a power of neutralizing certain toxins, and a nutritive and motor

[1] *British Medical Journal*, May 30, June 6, 1908.
[2] *Ziegler's Beiträge*, 1905, Band xxxviii.
[3] *Archiv f. exp. Path. u. Pharm.*, 1900, xliii, 321.
[4] *American Journal of Physiology*, 1901, vol. iv.

stimulating substance. Extirpation of the adrenals is followed by the compensatory hypertrophy of accessory glands, mainly cortical in structure, and injections of the medullary pressor substance cannot keep alive animals deprived of the glands. It has been supposed that the cortex has a part in the beginning of the elaboration of the pressure-raising substance.

Relation of Disordered Adrenal Function to Disease.—It is evidently too early to describe the diseases of the adrenals and the chromaffin system on the basis of altered function, but attention should be drawn to the beginning made in that direction. Many French investigators ascribe three histological divisions and three sets of functions to the glands. (1) The cortical cells, producing among others a lecithin body, having a myotonic function; (2) the chromaffin cells of the medulla, making adrenalin, with its hypertensive and angiotonic function; (3) sympathetic cells in the medulla with important nervous relations. Bernard and Bigart suggest the terms "hyperepinephry" and "hypo-epinephry," to distinguish clinical features due respectively to excess or deficiency of adrenal function and including the possibility of relative excess or deficiency from the abnormal amount or character of antagonizing secretions. Hypo-epinephry or adrenal inadequacy is distinguished from Addison's disease by the absence of pigmentation. Hyperepinephry is impossible at present to distinguish from other cases of high arterial tension. Vaquez's idea of the adrenal origin of hypertension makes the distinction superfluous, if we can only exclude all other causes of high tension, but the evidence at present is conflicting.

Hypo-epinephry, adrenal inadequacy, is easier to circumscribe, at least theoretically, and occurs in three chief forms, acute, subacute, and chronic. The former includes the "pseudoperitonitic" form of Ebstein, the "pseudocholeraic" form, and "pseudomeningitic" form of Sergent. The subacute forms last from a few weeks to a few months; the chronic cases are equivalent to so-called partial Addison's disease. The essential features are myasthenia and hypotension, the systolic pressure usually being below 100 mm. of mercury. Other symptoms are: Hyperæsthesias, pains in the lumbar region or elsewhere, headache, delirium and coma, digestive disturbances, sudden death, with or without previous symptoms. Sergent[1] describes a vasomotor phenomenon which he calls the "white line," a pale area appearing in one-half to one minute after scratching the skin, and lasting for several minutes. Le Clerc denies its value. Dufour and Rogues,[2] Fursac and Schneider[3] give hypo-epinephry an important role in the production of neurasthenia, others ascribe to it the low arterial pressure of cirrhosis of the liver (Ferrannini), or the nervous symptoms of movable kidney (Championnière). The future must show the real relations.

There are many evidences of a close relation between the adrenals and various other ductless glands. Animal experiments suggest a relation between the sexual organs and the adrenals. Marchand's case of feminine hermaphroditism with atrophy of the ovaries and hyperplasia of the adrenals, and Bossi's case of osteomalacia improved by adrenalin are cited to confirm this. Many examples of a relation between growth and the adrenals have been published, especially the celebrated case of Linser, in which a boy aged five and one-half years, with hypernephroma, resembled one of sixteen to eighteen years. Other examples will be mentioned under Anomalies.

[1] *Presse Médicale*, November 15, 1903.
[2] *Archives générales*, 1904, p. 1533.
[3] *Rev. de Méd.*, 1907, p. 970.

Such facts as the pigmentation of Basedow's disease and the coincidence of that with adrenal disease suggest the relation of the adrenals and the thyroid. Pansini and Benenati saw a case in which there was tuberculosis of both adrenals, Addison's disease, enlargement of the once atrophied thymus, hypertrophy of the thyroid, pituitary, and spleen. Persistence of the thymus has probably been too little recognized in many cases hitherto examined, so that it can hardly be discussed at present. The resemblance of the structure of the hypophysis and adrenal and the occurrence of chromaffin tissue in the former lead to the view of a close relation here. There can be no doubt of a close relation between all the ductless glands, as well as one between the latter and other organs, but this has not yet reached a stage permitting a systematic survey. Those who wish to get a larger view should consult the monumental work of Sajous, as well as many shorter articles.[1]

ANOMALIES OF THE ADRENALS.

Absence of the adrenals has been noted, but at a time when no attention was paid to possible compensating adrenal tissue. *Hyperplasia* of the cortex was seen by Marchand in a case of defective development of the genitals, with accessory adrenal in the broad ligament.

Hypoplasia has been noted, and is important on account of its relations. It has been found with hemicephaly and other failures of development of the brain, with retarded sexual development, osteogenesis imperfecta, and osteomalacia. Czerny has seen absence of the medulla in 5 cases of hydrocephalus; Hansemann, 8 cases of anencephaly with atrophy. Wiesel observed hypoplasia of the chromaffin system with hypoplasia of the vascular system and other changes, and in one case status thymicus and sudden death with hypoplasia of the medulla of the adrenals, and also once in a fatal case of sunstroke. Carl Hart found the adrenals enlarged in animals injected with the juice of a persistent thymus.

It is noteworthy that in cases of movable kidney the adrenals remain in the normal position. In cases of renal tumor they are sometimes displaced. Anomalies of position are rare. Pilliet found the right adrenal under the fibrous capsule of the kidney. Horseshoe adrenals have been seen (Orth).

Compensatory hypertrophy of an adrenal gland has often been observed in case of disease (Durst, Simmonds) or faulty development of the other. Neusser states that both cortex and medulla are affected; Karakascheff found only the cortex hypertrophied, as appears to be the case in experiments on animals. In a case of tuberculosis of both adrenals, Wiesel found hypertrophy of chromaffin tissue outside the adrenals, especially in large amounts on the solar plexus.

In future the finding of anomalies of the adrenals should lead at once to the careful examination of the whole chromaffin system, as well as to the search for cortical adrenals and the examination of the other ductless glands.

[1] D. H. Rolleston, "Some Problems in Connection with the Suprarenals," *The Lancet*, September 28, 1907, ii. C. E. de M. Sajous, *The Internal Secretions and the Principles of Medicine*, 1903, 1907. L. Bernard, "Du role des glandes surrénales dans les états pathologiques," *Revue de Méd.*, October 10, 1907, p. 977. Eppinger, Falta, and Rudinger, "Ueber die Wechselwirkung der Drüsen mit innerer Sekretion," *Zeitschrift f. klin. Med.*, 1908, Band lxvi, pp. 1 to 200.

INFECTIONS AND INTOXICATIONS.

These affect the adrenals sometimes alone, sometimes along with other organs, in varying degrees of intensity. The anatomical changes in such cases are either congestion, hemorrhage, or infiltration. Such changes are found in experimental diphtheria, tetanus, anthrax, pneumonia, etc. In rabies, on the contrary, reactive processes were found by Morchini, Langlois, and Lubarsch, and Elliott and Tuckett found that in cases of infection of the glands the adrenalin was diminished. An antitoxic action, if present, does not coincide with increased blood pressure raising function, but the reverse. "There is no proof that the adrenals play a part in the defence of the organism against infection" (Bernard). In men Oppenheim and Loeper found lesions similar to those in experiments on animals. The effect upon the symptom complex in such cases is, of course, impossible to determine with our present methods. In some cases the loss of adrenalin may be suspected, as in a case of Sergent, in which a man with pneumonia and marked depression had hemorrhagic inflammation in both adrenals. Sicard made a diagnosis of adrenal insufficiency in a case of bronchopneumonia with extreme asthenia, diarrhœa, low temperature, and blood pressure 7.8 by Potain's sphygmomanometer, in which adrenal hemorrhages were found.

Intoxications also affect the adrenals. The action of mercury is unsettled. In lead poisoning, which causes hyperepinephry in guinea-pigs (Bernard and Bigart), Gouget thinks the atheroma is brought about by the agency of adrenalin. In a case of lead encephalopathy, however, Ménétrier found the adrenals normal and no atheroma of the aorta. Biliary intoxication causes congestion and hemorrhage, stimulation of the cells in acute cases, depression in chronic ones (Bernard and Bigart). The melanoderma, low blood pressure, and asthenia of jaundice might be explained in this way (Gilbert and Lereboullet, Gaudy, Gourand). Renal auto-intoxication has often been looked upon as a potent cause of adrenal disease. Bernard describes a cortical hyperplasia of the adrenals with renal disease, but does not think it the cause of high blood pressure.

Some practical outlooks may be obtained from the observations mentioned. If the low blood pressure of many infectious diseases is due to adrenal inadequacy, adrenalin could be used to counteract it. Grünbaum suggests using adrenalin as a diagnostic measure—healthy people show no effect on the blood pressure, but those with adrenal inadequacy do. Rolleston has used adrenalin in pneumonia and bronchopneumonia to prevent cardiac failure, and has had no bad results, such as pulmonary œdema, that would suggest failure of the left heart from obstruction. The temporary use of the remedy in such cases would not be likely to be followed by arterial degeneration.

CIRCULATORY DISTURBANCES OF THE ADRENALS.

Anæmia of the adrenals is of no clinical significance, and the same is true of anæmic necrosis.

Hyperæmia is frequent, especially the passive form, as a result of disease of the heart and lungs. Active hyperæmia occurs in infections, especially diphtheria, typhoid fever, pneumonia, erysipelas, and smallpox. Both of

these forms are likely to be associated with hemorrhages. The latter may also be caused by trauma, by blood conditions such as leukæmia and hemorrhagic diathesis, thrombosis, and embolism. It is common in stillborn children. Males are affected oftener than females.

Hemorrhages may be capillary and punctate, few or many, and may be of any size, even up to that of a man's head. They are unilateral or bilateral, the right side being more often affected than the left. The blood undergoes the usual changes, and the reaction around the focus varies with the amount of blood and the conditions associated with the hemorrhage. In cases with recovery absorption and calcification occur, with more or less fibrous tissue in the vicinity.

Symptoms.—Virchow, who first called attention to the subject, described severe symptoms of the typhoid state, and signs of peritoneal irritation and convulsions, soon fatal. Karakascheff emphasized asthenia and intestinal irritation. In Munson's[1] case myasthenia was not specially marked. According to Rolleston[2] the most characteristic symptoms are: "Sudden onset with fever, violent pain in the hypochondrium radiating to the loins, convulsions, vomiting, diarrhœa, and later tympanites, collapse, and death within forty-eight hours from the onset." Some of the phenomena are doubtless due to damage to the abdominal sympathetic, producing symptoms like those of hemorrhagic pancreatitis or ileus. Purpura sometimes occurs, especially in children, along with fever and convulsions, suggesting an acute exanthem (Munson), and it has been suggested (Dudgeon[3]) that purpura is the expression of acute destruction of adrenals, as pigmentation is of the chronic kind. Arnaud describes a group of cases without bronzing of the skin, but with other evidences of chronic inadequacy of the adrenals.[4]

INFLAMMATION OR SOFTENING OF THE ADRENALS.

Various forms of inflammation of the adrenals have long been described, but the subject has acquired a new importance from work instigated by Lubarsch. It will be remembered that the name of "suprarenal capsule" was given because of the frequent presence of a cavity in the organ. At a later period, this was looked upon as the result of portmortem softening, without distinct pathological relations. Lubarsch was impressed by the fact that the change was not parallel to other postmortem alterations, and at his suggestion E. Rosenstein[5] made an investigation, as the result of which he came to the following conclusions:

"Softening and cavity formation of the suprarenal glands is not a pure postmortem phenomenon, due to decomposition. As a rule, disturbances of circulation, especially acute inflammatory conditions at the boundary of the cortex and medulla, prepare the way for the softening. Inflammatory changes of the suprarenal glands are much more frequent than is usually supposed, and appear both as exudative and productive processes. Most lung

[1] *Journal of the American Medical Association*, July 6, 1907, p. 19.
[2] *Loc. cit.*
[3] *American Journal of the Medical Sciences*, 1904, cxxvii, 134.
[4] See the excellent study of R. S. Lavenson, "Acute Insufficiency of the Suprarenals," *Archives of Internal Medicine*, 1908, ii.
[5] *Arbeiten aus den path. anat. Abth. der K. hyg. Inst. zu Posen*, 1901, p. 116.

diseases, especially tuberculosis and pneumonia, advanced arteriosclerosis and heart disease—in short, diseases prone to abdominal engorgement—favor the process, while in anæmia, including pernicious anæmia and amyloid disease, the suprarenals are intact. The cavity formation occurs equally on both sides (and so cannot be due to bile imbibition) as small or large cavities, visible at once on sectioning or upon slight pressure. The cavities may be found from six to fourteen hours postmortem, the usual time for making the autopsies, but cavities are indicated two and one-half hours after death. Macroscopically, the medulla is wholly or partly absent in case of large cavities, the cortex narrower than normal. Microscopic examination shows ragged walls formed of normal medulla or cortex. The veins remain passing through the cavities. Inflammatory changes are not always present, but their frequency in cases in which cavities are found early seems to point to a relation."

Abscesses are found in the adrenals in cases of inflammation in the vicinity or in septicopyæmia, rarely primary, as in the remarkable case of Janowski.[1] In this, weak pulse and heart and dark brown urine were striking symptoms. When the inflammatory process is limited in size, healing occurs, with more or less scar tissue.

Symptoms.—The symptoms of acute inflammation are at present impossible to distinguish from those caused by other processes in the primary diseases. Asthenia, subnormal temperature, low blood pressure, and sudden death do not usually permit a diagnosis of adrenal involvement, although in some cases the course of the symptoms may enable a probable diagnosis to be made. In chronic inflammation with cirrhosis, the syndrome of Addison is present.[2]

TUMORS OF THE ADRENALS.

Hypernephroma.—The adrenals, like the kidneys and other parts of the urogenital tract, are often the seat of neoplasms, usually small, fatty looking, with a fibrous capsule and the microscopic structure of the cortex of the adrenals in most cases, although medullary hypernephromas have been described (Manasse, Berdez). They have been called adenoma, or adrenal struma, but hypernephroma is preferable. For the most part they are benign and discovered by accident at autopsy. Warthin[3] has reported a case in which, with adenomas of both adrenals, there was degeneration of the adrenals of Marchand. They may set up metastases without giving evidence of local malignancy, or the latter may occur, causing large tumors of marked peripheral growth, invading neighboring organs, including blood-vessels.

Malignant Tumors.—Malignant tumors of the adrenals have been described under the names of carcinoma and sarcoma. Morphologically both forms occur, and may pass into each other, or one with carcinoma structure may have sarcomatous metastases. The pathology of these growths has been the subject of much investigation, which is well utilized in the study

[1] *The Lancet*, July 23, 1898.
[2] See E. Sergent, *Archives gén. de Méd.*, 1904, p. 14.
[3] *Archives of Pediatrics*, 1901.

of Woolley,[1] who prefers the term mesothelioma to any of the other names. A good many tumors of the chromaffin tissue, in the adrenals as well as elsewhere, have been reported. They have been called peritheliomas, gliomas, sarcomas, etc. In all such cases the chromic acid reaction should be used to determine the specific character of the cells. Rolleston and Mulon have called attention to the resemblance of adrenal cortical cells to "luteal cells."

All the malignant tumors of the adrenal are remarkable for their high degree of vascularity and their tendency to fatty degeneration. The combination predisposes them to hemorrhage, and they often form large cysts—nine pints of fluid were removed from one by McCosh—with contents more or less degenerated, formerly spoken of as "hemorrhagic cystic adrenal struma" (Henschen[2]).

Symptoms.—The symptoms of adrenal tumor are of great variety. In one case Woolley observed excessive development of the genitals, hair, and fat. Bullock and Sequeira have collected 10 similar cases—8 females—in children. In these cases the tumors seemed to be cortical, while in 12 of probably medullary origin there was not precocious development. There are rare cases, like those of Richard and Thornton, of hypernephroma in adults, with excessive growth of hair. However, precocity of growth is not always due to adrenal growths.(Guthrie and Emery). According to Cooper, tumors of the right adrenal frequently press upon the cava; those of the left are in relation to the stomach. Cortical hypernephromas have a tendency to metastasis in certain localities, as the vertebræ, skull, head of the femur, clavicles, and brain.

R. Hutchison[3] has called attention to cases of sarcoma of the adrenals with metastases of the skull, ribs, sternum, and vertebræ, but not in the long bones (?), with proptosis, discoloration of eyelids, severe secondary anæmia, without leukocytosis or signs of increased intracranial pressure, and running a rapid course. The histological type may not be fixed. Some of the tumors may have been hypernephromas. In some cases of hypernephroma symptoms of Addison's disease have been observed. In some cases the symptoms have improved after operation (Bittorf). It is possible that the symptoms are due not to secretions, but to the toxic substances liberated by the breaking down of the tumors. Neusser has thought that in some cases of adrenal tumors there was hypersecretion.

Diagnosis.—The diagnosis of adrenal tumors is often difficult. They are generally mistaken for renal tumors. H. Morris points out as useful signs their mobility, rapid growth, and the tendency to varicocele on the same side. The tumors often press upward. Israel[4] describes five groups. In the first there is no tumor, no symptoms of adrenal disease, but metastases. In the second, no tumor, but signs of adrenal disease, such as hæmaturia, paroxysmal pains, and paræsthesias in the region of the lumbar plexus or the tenth dorsal nerve. In the third group there is a palpable tumor, but the kidney cannot also be palpated. In the fourth, both tumor and kidney are palpable. In the fifth group both organs are grown together. Fever is

[1] *Transactions of the Association of American Physicians*, 1902.
[2] *Beiträge zur klin. Chirurgie*, 1906, vol. xlix.
[3] *Quarterly Journal of Medicine*, 1907, i, 33. See also the valuable article by Tileston and Wolbach, *American Journal of the Medical Sciences*, 1908, cxxxv, 871.
[4] *Deutsche med. Woch.*, 1904, No. 44.

an important symptom, occurring in 50 per cent. of cases. As the case of Schnittenhelm shows, the pulse may not suggest the condition, and severe symptoms may come on late and suddenly. Tumors of aberrant adrenal tissue present symptoms according to their location chiefly. Those in the kidney and liver are clinically most important.

Prognosis.—The prognosis of adrenal tumors is bad, largely on account of the late diagnosis, rapid growth, and tendency to metastasis.

TUBERCULOSIS OF THE ADRENALS.

Tuberculosis of the adrenals is especially important on account of the relations to Addison's disease, but its general features may be mentioned here. Miliary tuberculosis is less frequent than the diffuse or nodular and caseating forms. Either form may effect one or both adrenals. Men are more often affected than women; the ages from thirty to sixty are especially concerned. The infection is usually secondary, from tuberculosis of the lungs, bronchial glands, intestines, genital organs, kidney, or vertebræ. It is sometimes primary, and may set up miliary tuberculosis. More frequently groups or single miliary tubercles in any part of the gland caseate and undergo fibrous degeneration, which spreads into the adjacent tissue. Fresh tubercles may follow in crops, causing sometimes extensive changes in the neighboring organs. Tuberculosis of the peritoneum often follows. Amyloid degeneration is often present. Pigmentation of the skin is relatively rare, especially with one-sided lesions.

SYPHILIS OF THE ADRENALS.

Syphilis of the adrenals is rare, but has been seen in both congenital and acquired forms of the disease. Sclerosis usually follows.

ADDISON'S DISEASE.

Synonyms.—Bronzed skin disease. Melasma Addisonii seu suprarenale, morbus Addisonii (Lat.); asthénie surrénale, melanodermie asthénique, maladie bronzée, maladie d'Addison (Fr.); Addison'sche Krankheit (Germ.); morbo di Addison, malattia di Addison (It.); enfermedad de Addison ò bronceada (Sp.).

Definition.—Addison's disease is characterized clinically by pigmentation, muscular and vascular weakness, disturbances of the gastro-intestinal tract and nervous system, and other symptoms, and anatomically by disease of the adrenal glands.

Historical Note.—Although the occurrence of alterations in the adrenals was known before the time of Thomas Addison,[1] he not only gave so accurate a description of the clinical features of the disease that nothing essential has been changed, but also made a remarkably accurate attempt at defining

[1] *On the Constitutional and Local Effects of Disease of the Suprarenal Capsules*, London, 1855; also in his "Published Writings," New Sydenham Society, 1868.

its anatomical basis. It was, therefore, proper to give his name to the disease (Trousseau, 1856). Notwithstanding the skeptical attitude of some great authorities, observations multiplied rapidly, considering the rarity of the disease. Isaac Taylor[1] reported a series of cases in New York in 1856. The labors of Sir Samuel Wilks, Jonathan Hutchinson, and E. H. Greenhow had wide influence in stimulating clinical and anatomical observations. Brown-Séquard's experiments on animals were too far in advance of their time, but within the last quarter century this part of the subject has been prosecuted with brilliant but as yet imperfect results. Important landmarks in the history of the disease were made by the works of Averbeck (1869) and G. Lewin;[2] the experiments of Tizzoni (1889); Abelous and Langlois (1891–1892); and the systematic works of E. Neusser,[3] Byrom Bramwell,[4] and H. D. Rolleston.[5] Finally, a new epoch has been made by the discoveries and investigations of Kohn, Wiesel, and others, mentioned above.

Pathogenesis.—The imperfections in our knowledge of the functions of the adrenal glands are such as to prevent the formulation of a satisfactory theory of Addison's disease, and the difficulty is increased by the incompleteness of anatomical investigations up to the present time.

Addison at first believed that the peculiar symptom complex could be caused by any morbid condition of the adrenals. Wilks and Greenhow emphasized the importance of the sympathetic nerves. Addison later assigned them part of the morbid action, and as the adrenals were for a time looked upon as a part of the sympathetic system, this view became very prominent. Von Kahlden, at first an advocate, later discarded the sympathetic theory. As the internal secretions became more conspicuous, the nervous theory was displaced by theories of adrenal auto-intoxication on the one hand, adrenal arrest or inadequacy on the other.

From a recent critical study of his own and selected reported cases, A. Bittorf[6] comes to the conclusion that disturbance of the adrenal function is the sole cause of Addison's disease. The disturbance of function can arise either from disease of the glands or from disease of the secretory nerves. So, apparently normal glands may have disturbed functions (probably with slight but hitherto undemonstrated lesions). Such cases are probably rare, but Bramwell has cited two in which pseudoleukæmic growth involved the sympathetic nerves. Bittorf discusses the apparent contradictions of cases of tuberculosis with symptoms and of cancer of the glands without symptoms; of Addison's disease with no lesions of the adrenals and of adrenal disease without symptoms; of disease of one adrenal with symptoms. Inasmuch as in many cases the full relations, and especially the conditions of aberrant adrenal tissue are not stated, all such discussions are open to a serious fallacy.

The explanation of single symptoms is also unsatisfactory. Thus, low blood pressure, asthenic and cerebral symptoms may be due to lack of

[1] *New York Journal of Medicine*, September, 1856, p. 153.
[2] *Charité Annalen*, 1884–1892, vols. ix, x, xvii.
[3] *Nothnagel's spec. Path. und Therap.*, 1897, vol. xviii, Pt. 3.
[4] *Anæmia and Some of the Diseases of the Blood-forming Organs and Ductless Glands*, 1899.
[5] *Allbutt's System*, 1900, vol. v.
[6] *Die Pathologie der Nebennieren und Morbus Addisonii*, Jena, 1908.

pressor substance, but may equally be toxic. Pigmentation, explained by Rendle Short,[1] by lack of the pressor secretion, occurs in cases in which the blood pressure is not demonstrably low. Bittorf mentions two cases, and the writer has seen a characteristic pigmentation of the skin and mucous membranes with a maximum pressure of 145 and minimum over 100, with only moderate asthenia. Inasmuch as the normal processes of pigmentation are unknown, any theory of Addisonian pigmentation must at present be unproved.

In general, Bittorf's conclusions are of considerable clinical value. He believes Addison's disease with all its symptoms the result of adrenal disease. The symptoms depend, according to him, upon a gradual and ultimately complete arrest of adrenal function, possibly partly due to temporary qualitative alterations. He admits that the functional disturbance in some rare cases may possibly be due to disturbances of the secretory nerves, the glands being anatomically intact. Simple functional inadequacy he thinks as yet unproved. In the majority of cases there is a more or less extensive destruction of the adrenals. The alterations of the sympathetic nerves he thinks not significant either as regards the pathogenesis or the individual symptoms. Destruction of only a part of the gland is also relatively unimportant; the total function is the essential factor.

The chromaffin theory of Addison's disease is so recent that its real value cannot be stated. It must be taken into account, however, in future. The work of Wiesel[2] is fundamental, and, although based upon a small number of cases (seven), makes control investigations by the same methods necessary to all who would criticise it. His method of examination consists in the removal of almost the whole sympathetic system—the two adrenals, two chains of ganglia, the large thoracic, abdominal and pelvic plexuses, the hila of the kidneys and the surrounding fat and connective tissue in which chromaffin bodies and (cortical) adrenal tissue are found, and the tissue around the origin of the inferior mesenteric artery, containing Zuckerkandl's organ. The tissues, after naked-eye examination, are fixed in potassium bichromate and formalin solution, later bichromate solution alone. Frozen sections are made after fixing and examined for fat and lipochrome. Many sympathetic ganglia are cut in two, and one-half is hardened in 95 per cent. alcohol as a control to the bichromate sections.

Wiesel's results show that in Addison's disease the chromaffin cells have disappeared in the sympathetic system, and the medullary substance of the adrenals is intensely involved. Cortex and accessory cortical adrenals are not affected, or not extensively. The ganglion cells show the chromaffin reaction, which they do not in other diseases. Wiesel, therefore, looks upon Addison's disease as a specific affection of the chromaffin system. It consists, according to him, of a successive atrophy of chromaffin tissue, which, in the adrenals, spreads to the cortex. To compensate for the loss of chromaffin tissue some of the ganglion cells become chromaffin. The absence of symptoms of Addison's disease in some cases of extensive adrenal tuberculosis can be explained, as in a case of Wiesel's, by preservation of the chromaffin system. The medullary portion of the glands may be destroyed, but the remaining portion of the sympathetic system is intact, and sufficient chrom-

[1] *Lancet*, 1906, ii.
[2] *Zeitschr. f. Heilkunde*, 1903, Band xxiv; *Path. anat.*, Abt. No. 4.

affin tissue remains to prevent the specific symptoms. On the other hand, Addison's disease may exist without disease of the adrenals. The fact that perfect compensation does not occur Wiesel explains by the limited number of changed ganglion cells. The disease affecting the chromaffin system is oftenest tuberculosis, but it is not yet known whether other disturbances can produce the same results. Not all the symptoms can be explained on the chromaffin theory, the pigmentation being a stumbling block, as under other theories. The asthenia is easy to explain.

Beitzke[1] has reported a case of carcinomatous destruction of both adrenals, but with chromaffin tissue preserved in the sympathetic, without Addison's disease.

Pathology.—**The Adrenal Glands.**—In the great majority of cases there is a lesion of the adrenals. Lewin, in his analysis of the literature up to 1892, found the adrenals diseased in 88 per cent. and "healthy" in 12 per cent. In 28 per cent. of cases of adrenal disease he found no history of pigmentation. On account of the sources of the histories these figures have only a general application.

The most frequent change is tuberculosis, which usually affects both glands, sometimes only one. It occurs in the adrenal primarily in some cases (Marchand, Chvostek, and others), more frequently with tuberculosis of other parts of the body, especially the lungs, genito-urinary tract, bones, peritoneum, etc. The most frequent change is widespread or complete caseation, with tubercle bacilli still present, and softening, fibrosis, or calcification. Sometimes there are groups of tubercles in various stages of degeneration, in the cortex, medulla, or on the surface, and invading the adjacent tissues. Sometimes there are very few tubercles or their remains, but old and more or less widespread fibrosis or adhesions. In rare cases tuberculous tumors are found, up to 60 grams weight in one case (Alezais and Arnaud).

Next in importance to tuberculosis is atrophy, which has recently been carefully studied by Bittorf. In most cases the process is a simple atrophy or chronic interstitial inflammation with retraction and destruction of the parenchyma, resembling sclerosis of other parenchymatous organs. In simple atrophy the glands are more or less diminished in size, and sometimes as thin as paper. The general shape may not be much altered, or the gland may be represented by a small mass of fat. The color varies; the consistence is rarely altered. One adrenal may be wholly absent, even to its afferent vessels. Microscopically, the tissue is absent in one or more layers, or there is fatty degeneration, atrophy, or necrosis. Sometimes alterations are few, the chief abnormality being aplasia. Inflammatory alterations are absent or slight, but lymphocyte foci sometimes occur. According to some observers these are normal features of the adrenal. The vessels are sometimes normal, in other cases wide, or narrow, or atrophic. The nerves and ganglia in the glands are sometimes well preserved, sometimes atrophic.

The inflammatory atrophy of the adrenals leads to retraction and induration, sometimes with widespread fibrosis of the surrounding tissue. One or both glands or part of one gland may be involved. Microscopically there is fibrous tissue in strands, among the cell columns, resembling the appearance of a cirrhotic liver. The cells show various forms of degeneration, and there are also lymphocyte or polynuclear foci. Both arteries and veins

[1] *Deut. med. Woch.*, 1904, p. 897.

are often thickened, especially in the intima. In rare cases inflammatory processes, possibly traumatic, cause tumor-like enlargements.

Carcinoma has been observed with Addison's disease by several observers, also sarcoma, melanotic tumors, hypernephromas, and peritheliomas. Syphilis has been noted, usually in the form of gummas with caseation, fibrosis and infiltration of the adjacent structures. Other lesions are: Cavernous angioma, mycosis fungoides, and echinococcus.

Sympathetic System.—The solar plexus and semilunar ganglia, as well as the ganglia and nerves in the adrenals, are often the seats of alterations in Addison's disease. They may be atrophied from the pressure of tumors, affected by tuberculosis by extension or as part of a widespread invasion, or they may be involved in inflammatory processes.

Besides these changes, various others have been described, such as pigmentation atrophy, small-celled infiltration, vascular changes, and fibrosis of the ganglia and nerves. Edel found the solar plexus and semilunar ganglia embedded in a fibrous mass. Fleiner found degenerative changes in the spinal ganglia, posterior roots, and cord, Miklassewski in the intervertebral ganglia. But in most cases the changes are not severe, and many investigators have found few or none. This corresponds to the negative results of all who have attempted to produce the disease by extirpation of the sympathetic ganglia. The changes in the chromaffin system have been mentioned.

Brain and Cord.—In the spinal cord degenerations of various columns, infiltrations, thickening of the bloodvessels, and changes in ganglion cells have been described, but they are not peculiar to Addison's disease and have no significance in most cases. In the brain, œdema and other common vascular alterations occur. Tuberculosis of the brain or meninges may be an accidental finding.

Thyroid Gland.—The thyroid gland has sometimes been the seat of alterations, usually diminution rather than enlargement. Persistent thymus has been observed, but not so uniformly as to suggest an important relation to the disease. The pituitary gland is not essentially affected.

In tuberculous cases the lungs, bronchial and mediastinal glands, genitourinary tract, and lymph glands are often involved. The lymphoid tissue in the spleen is often increased, the organ in general enlarged.

Heart.—The heart is often in a state of brown atrophy; arteriosclerosis is rarely present in a marked degree.

Stomach and Intestines.—The stomach and intestines frequently show such changes as are found in various diseases with the local symptoms that occur in Addison's disease. Congestion, increase of mucus, and ecchymoses are not uncommon. The Peyer's patches and lymphoid tissue in general are hyperplastic, sometimes ulcerated. Tuberculosis of the intestines sometimes occurs. Pigmentation of the peritoneum, noted by some authors, is not considered of importance. The same is true of pigmentation of the pia mater. Pigmentation of the mucosa of the intestine is probably rare to the extent described by Allchin.

Skin.—The pigmentation of the skin and mucous membranes has been the subject of very extensive investigations. Most observers look upon the pigmentation merely as an exaggeration of the normal process. The pigment is found in the cells of the rete Malpighii, sometimes in the corium. In the mucous membranes it occupies a similar position. Pförringer, in the skin, and von Kahlden, in the mucosa of the tongue, found pigment granules in

the vessels and in the tissue, free or in blood cells. An origin from the blood, however, is denied by Nothnagel, von Kahlden, and others, and many believe, with Pansini and Benenati, that the pigment is formed by the cells of the rete Malpighii. It does not contain iron. Carnot looks upon the pigment as a toxic substance, under normal conditions destroyed by the adrenals.

Etiology.—Addison's disease is rare in general. It affects all races, climate, and countries, but is thought to be more frequent in the white race and in Europe. It affects men somewhat oftener than women (6 to 4). The ages most affected are from 15 to 60. Cases sometimes occur in childhood, as early as the third year, and it may be congenital, as in a case reported by Osler; it has been seen as late as the eightieth year.

From what has been said of the pathology, it is clear that the causes sometimes assigned—malaria, alcoholism, cold, trauma, emotional strains, childbirth—may be admitted, but actual cases are rare in which they have a definite value. Tuberculosis and syphilis have their specific causes. The majority of cases come from the working classes, but others are by no means exempt. Heredity is obviously of little importance, but the disease has been seen in brothers (Tscirkoff, Andrewes), and in a mother and children.

Symptoms.—Clinical Features.—For the general picture of the disease it is impossible to improve upon the words of Addison: "The patient, in most of the cases I have seen, has been observed gradually to fall off in general health; he becomes languid and weak, indisposed to either bodily or mental exertion; the appetite is impaired or entirely lost; the whites of the eyes become pearly; the pulse small and feeble, or perhaps somewhat large, but excessively soft and compressible; the body wastes, without, however, presenting the dry and shrivelled skin and extreme emaciation usually attendant on protracted malignant disease; slight pain or uneasiness is from time to time referred to the region of the stomach, and there is occasionally actual vomiting, which in one instance was both urgent and distressing; and it is by no means uncommon for the patient to manifest indications of disturbed cerebral circulation.

"Notwithstanding these unequivocal signs of feeble circulation, anæmia, and general prostration, neither the most diligent inquiry nor the most careful physical examination tend to throw the slightest gleam of light upon the precise nature of the patient's malady; nor do we succeed in fixing upon any special lesion as the cause of this gradual and extraordinary constitutional change.

"We may, indeed, suspect some malignant or strumous disease—we may be led to inquire into the condition of the so-called blood-making organs—but we discover no proof of organic change anywhere; no enlargement of spleen, thyroid, thymus, or lymphatic glands; no evidence of renal disease, of purpura, or previous exhausting diarrhœa, or ague, or any long-continued exposure to miasmatic influences; but with a more or less manifestation of the symptoms already enumerated we discover a most remarkable and, so far as I know, characteristic discoloration taking place in the skin—sufficiently marked, indeed, as generally to have attracted the attention of the patient himself or of the patient's friends.

"This discoloration pervades the whole surface of the body, but is commonly most strongly manifested on the face, neck, superior extremities, penis, and scrotum, and in the flexures of the axillæ and around the navel.

"It may be said to present a dingy or smoky appearance, or various tints or shades of deep amber or chestnut-brown; and in one instance the skin was so universally and so deeply darkened that but for the features the patient might have been mistaken for a mulatto.

"In some cases the discoloration occurs in patches, or perhaps, rather, certain parts are so much darker than others as to impart to the surface a mottled or somewhat checkered appearance; and in one instance there were, in the midst of this dark mottling, certain insular portions of the integument presenting a blanched or morbidly white appearance, either in consequence of these portions having remained altogether unaffected by the disease, and thereby contrasting strongly with the surrounding skin, or, as I believe, from an actual defect of coloring matter in these parts. Indeed, as will appear in the subsequent cases, this irregular distribution of pigment cells is by no means limited to the integument, but is occasionally also made manifest on some of the internal structures.

"We have seen it in the form of small black spots, beneath the peritoneum of the mesentery and omentum—a form which in one instance presented itself on the skin of the abdomen.

"This singular discoloration usually increases with the advance of the disease; the anæmia, languor, failure of appetite, and feebleness of the heart become aggravated; a darkish streak usually appears on the commissure of the lips; the body wastes, but without the emaciation and dry, harsh condition of the surface so commonly observed in ordinary malignant diseases; the pulse becomes smaller and weaker; and without any special complaint of pain or uneasiness the patient at length gradually sinks and expires."

Some writers have attempted to describe stages in the course of the disease, but so variable and at the same time insidious is the course in general that it seems better to consider the symptoms in detail, with reference to their variations.

Asthenia.—In most cases, whether tuberculous or otherwise, the earliest symptom is an unusual tendency to fatigue on bodily or mental exertion. In the beginning this is not uniform, and even in the most distinct asthenic periods does not oblige the patient to take to bed nor to describe the striking weakness that occurs later. By degrees the weakness and loss of energy become more marked. The patient loses all inclination to exertion, and may have periods in which it seems impossible to rise from the bed. This may last for many months before the other symptoms develop to an extent making diagnosis possible, although an intense asthenia should always raise the thought of Addison's disease.

Gastro-intestinal Symptoms.—Often absent, when they do occur these are of great diagnostic value. Sometimes the stomach is free from symptoms, or the appetite is even voracious; more frequently the appetite becomes capricious, meat being especially repugnant, or appetite fails. There is a feeling of fulness after eating, nausea, eructations, or pyrosis. Constipation is the rule in the early stages. Later, irregular attacks of vomiting and diarrhœa make their appearance. Pain in the epigastrium or hypochondrium, the lumbar or sacral region, sometimes occurs, and with the other symptoms suggests gastric crises. Tenesmus is sometimes present. In the later stages the appetite fails completely; vomiting is frequent, and with the diarrhœa hastens the loss of strength.

Pigmentation.—This may occur early, and be discovered by accident before the other symptoms have been clearly recognized. Early discovery is more likely if the pigmentation occurs in irregular patches without relation to parts ordinarily pigmented. When it occurs on the face, neck, and hands, the areolæ and genitals, it may reach advanced degrees without exciting comment, or it may even be looked upon as evidence of health. The parts usually exposed to light, then the areolæ, external genitals, axillæ, flexor surfaces of the joints, median line between umbilicus and pubes, are first and most affected. Parts pressed upon by clothing, prominences, as over the spinous processes and knuckles, become dark sooner or later. Pigmentation is sometimes absent where the skin is shaded by the hair, and Bernard mentions a case in which pigmentation was general except on exposed parts; in many cases the hairy scalp is also affected. Scars are sometimes pigmented, sometimes surrounded by a dark areola. The palms and soles are rarely pigmented. Thibierge and also Scheult have seen the negro skin made darker by the disease in the areas affected by Addison's disease.

The pigment varies in color in different cases. Addison was well aware of this, and the different names given to the color are not always the result of fancy. It may be from a pale brown to a deep brown, bronze, or chocolate, or from a pale dirty gray to an almost sooty black. The color is often darker where counterirritation has been used, but the writer cannot agree with Trémolière that intense pigmentation after a poultice or plaster is evidence of a latent adrenal insufficiency. The pigment is never uniform, but may be almost so, except for the areas that are usually darker. On the other hand, it is often intensely dark in small areas, like common moles, and it is often interrupted by areas of vitiligo, as Addison pointed out. These are often overlooked or considered as normal, but the characteristic curved outlines permit them to be easily recognized, as well as the darker color at the margin. Pigmentation of the mucous membranes is almost the rule, occurring on the lips at the margin of the skin, on the tongue, buccal mucosa, gums, eyelids, especially the edges, and sometimes on the conjunctiva. Sometimes it spreads out from the angles of the mouth or eyelids, in distinct streaks. It also occurs on the mucous membranes of the genitals. A continuous dark brown line on the gums, near the margin, is sometimes very striking. Generally the pigmentation of the mucous membranes is not diffuse, but occurs in spots or streaks. The nail bed and nails are sometimes pigmented, and the hair seems to have a darker tint, looking dirty or dusty.

Aside from the pigmentation, the skin, as a rule, is smooth and elastic. Itching is rare, unless from complicating disease. Sweating is sometimes excessive, and the skin sometimes has a disagreeable fish-like odor. As rare complications in the skin, roseola, purpura, molluscum contagiosum, furunculosis, prurigo, and psoriasis have been described.

The "white line" is a very striking sign when present and deserves careful study. In a case seen by the writer with Dr. H. A. Freund, it came on slowly and remained many minutes, after scratching the skin, as a broad, chalky, white mark, but could be seen on uncovering the patient wherever a fold or wrinkle of the clothing had been in contact.

Nervous and Mental Symptoms.—The tendency to fatigue from mental and physical exertion has been mentioned. Besides this, a constant apathy often develops, and is sometimes associated with depression, insomnia, or

rarely increased tendency to sleep. Yawning is a marked symptom in some cases. Loss of memory, delirium, dizziness, tinnitus, and muscæ volitantes occur at times. Headache is frequent and sometimes violent. Diminished sensibility, or paræsthesia—formication or numbness—sometimes exists in the pigmented or leukodermic areas. In the later stages the asthenia reaches a striking degree. Although the patient may not look very ill, weakness is so intense as to make the slightest movement difficult or impossible. Syncope comes on with alarming ease, with or without nausea, vomiting, and cold perspiration, from exertion, a prolonged examination, a tuberculin injection, and sometimes from accidental or other pressure on the abdomen.

In some cases the mind is affected. There is loss of memory, or imbecility in various degrees, sometimes even dementia. Depression is more common than excitement, but restlessness and anxiety occur. Tremor and choreiform and epileptiform convulsions are rare. Weakness of the special senses, especially smell, taste, and hearing, is not uncommon.

Pain in the muscles and nerves is very severe in some cases, especially pain of a neuralgic character in the epigastrium and lumbar region, sometimes in the joints. The latter may be swollen (Ebstein), leading to the diagnosis of rheumatic arthritis. The reflexes show no characteristic change. They are often slow and weak.

Heart and Circulation.—Cardiac weakness is part of the picture of the disease. The heart beat and sounds are faint, the pulse small, soft, and usually slightly accelerated. Exertion is likely to bring on alarming dyspnœa and palpitation. Murmurs are not always present. The blood pressure is usually low, as has long been recognized by the touch; observations with the sphygmomanometer, first made by Charlewood Turner (1899) confirm it. In four cases personally observed the maximum systolic pressure was 110, 108, 85, and 82; minimum, 85, 75, 65, 60 respectively (Stanton instrument; 12 cm. band). The two cases with lowest pressure were seen only a few days before death. Janeway has reported a patient with a systolic pressure of 140. Grünbaum[1] uses the blood pressure and adrenal extract in diagnosis. In a suspected case, if the pressure is low, 3 grains of adrenal extract are given three times a day for three days by the mouth. A rise of more than 10 mm. makes adrenal insufficiency almost a certainty. The subject is thoroughly discussed by Parisot.[2]

The Blood.—Addison looked upon the disease as an anæmia, a view shared by many others and sometimes held even at the present time. In most cases, however, until the latest stages, marked anæmia is rare, or, if present, can be explained by complications, such as tuberculosis or cancer of important organs, or severe gastro-intestinal disturbances. The skin and mucous membranes are sometimes pale, suggesting pernicious anæmia, but in most cases pallor is not marked. Foersterling's case of bronze skin with pernicious anæmia and without macroscopic changes in the adrenals seems questionable. The usual conditions are illustrated by four fatal cases in the writer's clinic. These had red blood counts of 4,240,000 to 5,676,000 cells per cmm. The hæmoglobin was low in most cases—65, 82, 87, and 100 per cent. The leukocytes are not increased, as a rule, sometimes slightly diminished, and the differential count shows no constant change. Neusser looks upon

[1] *Practitioner*, August, 1907.
[2] Pression artérielle et glandes a sécrétion interne, Paris, 1908.

increase of lymphocytes as a bad omen. Large and small lymphocytes vary in different cases, and the total lymphocyte count may exceed that of the polynuclears. High red cell count and hæmoglobin are doubtless due in some cases to concentration from loss of fluid. Such cases have been carefully examined by Christomanos and Hamel, and the latter compares the condition to the combination of oligæmia and concentration of the blood sometimes seen in tuberculosis.

Abdominal Organs.—Besides the symptoms above mentioned, referred to the abdomen, more severe phenomena sometimes occur, such as pain or tenderness, diffuse or localized, and with rigidity of the abdominal wall. These symptoms excite suspicion of peritonitis, and in some cases are, in fact, associated with tuberculosis of the peritoneum. Ebstein and Zaudy report cases, with vomiting, going on to collapse, in which the cause could not be found. In some cases the pains are paroxysmal, and suggest crises of tabes or lead colic, while gallstones and gastric ulcer are often simulated by peculiar localizations of the pain.

Digestive Disturbances.—In rare cases of Addison's disease the stomach and intestines present no marked abnormalities. In the majority of cases there is more or less disturbance. Eructations, hiccough, and vomiting are frequent. The vomiting may occur with or without taking food. Remissions and exacerbations of the gastric symptoms are characteristic, especially in the earlier stages. In the later stage, vomiting becomes severe and painful, and hastens the fatal end. Mucus, bile, and traces of blood may then occur in the vomitus. Examination of the stomach contents usually shows no marked abnormality until an advanced period, when low or absent hydrochloric acid, diminished peptic power, and excess of mucus are encountered.

Constipation and diarrhœa occur in different cases in almost equal proportions, but constipation is more frequent in the early stages. Diarrhœa is sometimes profuse, rarely painful. The stools in such cases show mucus in excess, rarely blood. Tuberculosis of the intestine does not always cause distinct symptoms.

The liver and biliary tract rarely show clinical anomalies, and then only as complications. The spleen is sometimes enlarged.

In women amenorrhœa is a frequent symptom. Other menstrual anomalies are accidental. Tuberculosis of the uterus, tubes, and ovaries occurs in some cases. In men impotence has been observed. Tuberculosis of the epididymis may be a complication.

Urinary Organs.—Changes in the urine are neither constant nor specific. The quantity is sometimes diminished, sometimes increased. The specific gravity is rather low than high, the coloring matter not always increased. Indican and other coloring matter may be in excess in some cases. The finding of taurocholic and hippuric acid, of neurin, etc., has had no recent confirmation.

The metabolism is usually reduced, corresponding to the cachexia. Adrenal preparations affect the metabolic processes differently in the different cases.[1] Emaciation is slight, but loss of muscle tissue may involve considerable loss of weight.

The temperature, in the absence of complications, is apt to be subnormal. In rare cases hyperpyretic temperatures have been recorded, 111° F. according to Barlet and Lucas.

[1] Magnus-Levy, *Handbuch der Pathologie des Stoffwechsels*, 1907, Band ii, p. 352.

Varieties of the Disease.—There are many varieties of type, both as regards course and combinations of symptoms. Some cases are acute, ending within a few weeks from the first discovery of illness. Many such cases are really chronic, as may be discovered on careful inquiry. A sudden increase of weakness, or an acute attack on the part of the stomach or intestines, first reveals the alarming condition. As to the clinical picture, it is hardly necessary to point out the differences caused by preponderance or absence of cardinal symptoms—asthenia, pigmentation, and gastro-intestinal disturbances—nor is there any advantage in speaking of cases as "incomplete" or "fruste." There are some differences, depending on the age of the patient. Children are prone to gastro-intestinal symptoms, with asthenia, but with little pain, and to run a rapid course.

Diagnosis.—In some cases the diagnosis of Addison's disease is of the utmost simplicity. It can be made positively when we get a definite history of asthenia, vomiting, constipation and diarrhœa, pain in the abdomen and back; when we find pigmentation of the skin and mucous membranes, and when we can exclude visceral disease or blood disease (pernicious anæmia) that might account for a similar picture.

As the pigmentation is the most characteristic sign, it is well to consider first its use and value in the diagnosis. The most extreme pigmentation, in a person known to have been light-skinned previously, is rarely seen except in Addison's disease. Difficulties occur in cases in which the pigmentation is not so severe, or in which other causes for such a change cannot be excluded, and in which the other symptoms are not marked or their description not sufficiently clear. Even if the pigmentation cannot be assigned to any other cause, it is well to reserve the diagnosis until other symptoms, such as asthenia, can be positively recognized.

The other possible causes of pigmentation should be carefully considered. Difficulty is often experienced in patients with weakness and gastro-intestinal symptoms, sometimes neurasthenic, sometimes anæmic, by an unusual degree of pigmentation in areas normally pigmented—the areolæ, especially in women who have borne children and in old people, the median line of the abdomen, the axillæ and genitals. A knowledge of the existence of such conditions, based on inspection, will lead one to seek other evidences before making a positive diagnosis. Certain dark-skinned races, Chinese, Japanese, and Armenians, often have general pigmentation, increased in the usual areas, requiring a similar reserve. In both classes careful examination of the mucous membranes should be repeatedly made. Among negroes and in the yellow race (Japanese, according to Baelz) many healthy people have brownish gray or chocolate-colored spots on the lips, gums, and conjunctiva. In such cases the constitutional symptoms must be depended upon in the diagnosis of Addison's disease.

The pigmentation of pregnancy, not only on the areolæ, median line, and genitals, but also sometimes upon the face and neck, has been mistaken for that of Addison's disease, but careful examination, especially if repeated, can rarely leave any doubt as to the real condition.

Vagabond's disease, or a discoloration that occurs in people not actually vagabonds, from neglect, sometimes assisted by pediculi, simulates Addison's disease. The color is on the exposed parts, but the skin is rough and shows scratch marks, two signs rare in Addison's disease. The history, the absence of constitutional symptoms, or their explanation by other diseases,

and the effects of bathing, care, and nourishment, usually make the diagnosis easy. Roughness of the skin also excludes the mistaking of acanthosis nigricans for Addison's disease. Pediculosis and itching skin diseases sometimes cause pigmentation, but in these the scratches and the discovery of parasites or itching lesions prevent serious doubt. Hitschmann's case of pediculosis with pigmentation of the mucous membranes is a rare anomaly.

The pigmentation of malaria may cause difficulty, but the history, the condition of the blood in acute or chronic cases of malaria—so different from that of Addison's disease in the early stages—and the associated symptoms should enable one to avoid error. The pigmentation of syphilis and of scurvy can also usually be properly assigned by careful attention to the history and examination. Basedow's disease sometimes has a pigmentation resembling that of Addison's disease, but the other symptoms of the former are so clear that the only question would be whether there was a combination of both diseases, a point to be settled only by thorough examination and prolonged observation. In a case observed by Chvostek the pigmentation disappeared with the recovery of the exophthalmic goitre. The pigmentation of arthritis deformans should not lead to the diagnosis of Addison's disease in the absence of other symptoms.

Neusser, who has so thoroughly studied the skin changes in pellagra, points out the possibility of error in cases of diffuse pigmentation following erythema in the former disease. The pigmentation is sometimes macular. The erythema occurs chiefly in spring and fall; the mucous membranes are pale or livid; there is usually an intense anæmia, assisted in many cases by malaria and syphilis. Neusser found an increase of eosinophile cells in the blood and stools, and looks upon that as a useful point in diagnosis. The gastro-intestinal symptoms may be much alike in both diseases, although bulimia is more frequent than anorexia in pellagra. Careful attention to all the signs should prevent confusion between the two diseases.

Cancer and tuberculosis, with pigmentation, may cause error. In these the weakness in the later stages may suggest the asthenia of Addison's disease, but is rarely so extreme. In either case the adrenals may be involved, or the chromaffin or sympathetic system. When diagnostic difficulty occurs from either cancer or tuberculosis, the patient is usually in a stage where the exact diagnosis is not of therapeutic interest. F. Schultze has reported pigmentation of the tongue in cancer, an interesting observation, but one that raises the question as to a mechanism similar to that in Addison's disease.

Benign tumors of the uterus and ovaries are sometimes associated with an intense diffuse pigmentation of the skin, which disappears on removal of the growths. Other tumors with pigmentation, pelvic, pseudoleukæmia, melanosarcoma, can be recognized by care in the observation of other signs and symptoms. In cases with constitutional symptoms the possibility of adrenal involvement must be considered.

The pigmentation of bronze diabetes should be recognized by the enlargement of the liver and glycosuria. In marked cases the color of the skin is not so much like that of Addison's disease as it is like that from nitrate of silver. This latter pigmentation also is to be excluded by the history and the constitutional symptoms.

Arsenical pigmentation may at first glance suggest Addison's disease. The hypertrophic processes in the epidermis, as well as the history of arsen-

ical medication, may prevent error in some cases, but in cases of chronic poisoning from wall paper, food, or drink, the diagnosis may be very difficult. Neusser points out the difficulty of assigning the proper cause when a tuberculous patient, treated with arsenic, becomes pigmented.

Jaundice cannot easily be mistaken for the pigmentation of Addison's disease, but in the recovery from chronic jaundice, after the bile color has disappeared from the scleræ and mouth and from the urine, the face and hands often show a brown color unlike that in icterus. In such a case unless the history of previous icterus is clear, the diagnosis may present great difficulty. Gastro-intestinal symptoms may be described; weakness may exist. The absence of intense asthenia is important to note in such cases.

It is remarkable how many patients with vitiligo present themselves solely on account of the pigmentation associated with the leukoderma, and how often a diagnosis of Addison's disease is made in such cases. The recognition of the vitiligo should be easy, but it is necessary in all cases to exclude Addison's disease with vitiligo.

Pernicious anæmia, with or without arsenical treatment, sometimes has a diffuse or patchy pigmentation like that in atypical cases of Addison's disease. It may also be complicated with vitiligo. The weakness of the heart and muscles and the preservation of the subcutaneous fat, the gastro-intestinal disturbances, and absence of cause for the symptoms make a differential diagnosis difficult in cases without marked blood changes, or, if the latter are present, the combination of both diseases may be suspected. In case the mucous membranes are pigmented the diagnosis would be much more strongly warranted. Complete examination of the blood will put the diagnosis beyond doubt, and the possibility of the combination is then of scientific rather than practical interest.

In chronic interstitial nephritis in children Sawyer has observed a brownish discoloration of the skin resembling Addison's disease. Nothing abnormal was found in the adrenal bodies in cases examined postmortem. The differential diagnosis should present no great difficulty if the heart, arteries, and urine are examined.

Pigmentation of the mucous membrane is an important sign, but, like all others, is not infallible. In the first place, pigment spots occur in the mouth not only in some healthy individuals of dark-skinned races, but even in rare cases in Caucasians (Nothnagel, Eichhorst). On the other hand, pigmentation of the mucosa is absent in some cases of Addison's disease.

Even when pigmentation is marked and characteristic, a differential diagnosis is essential. When pigmentation is slight or atypical, we should suspect Addison's disease if there is marked or progressive loss of strength without emaciation, and without cause, or if there is tuberculosis. "The suspicion is strengthened if the patient is young (in other words, in cases in which obscure internal disease of a malignant kind is not likely to occur), if there is no profound anæmia, and if symptoms of gastro-intestinal irritation (which seem to be of nervous origin and which do not appear to be due to local stomach disease, such as simple ulceration) and lumbar pains are also present. It must be remembered that marked loss of weight (due to loss of muscle, but not to loss of fat) does not exclude Addison's disease" (Bramwell[1]).

In cases with pigmentation and no other explanation, but without asthenia

[1] *Clinical Studies*, 1904, ii, 257.

and gastro-intestinal symptoms, a positive diagnosis should not be given without careful investigation. In such cases the diagnostic injection of tuberculin may be cautiously used. In cases of Addison's disease even small doses of tuberculin may cause alarming symptoms. The conjunctival or cutaneous reactions could be used, but in all of these tests it is important to consider the possibility of latent foci of tuberculosis in other organs. A safer course would be to make a careful study of the blood pressure with and without adrenal preparations, and postpone tuberculin tests until the general condition of the patient is fairly well known.

The diagnosis of the anatomical condition, whether tuberculous, atrophic, or otherwise, cannot be made with accuracy, nor can the condition of the sympathetic, spinal nerves, etc., be safely included in the diagnosis. More complete studies of well-observed cases must be made before such diagnoses can be depended upon. The diagnosis of "adrenal insufficiency" in cases not well marked does not often seem of advantage. Such cases need careful investigation postmortem.

Prognosis.—Addison's disease is universally classed as a fatal affection; in fact, recoveries of genuine cases are so rare as to leave no other prognosis possible. And yet it must be recognized that if the primary lesion heals, if compensation can occur by the hypertrophy of other tissue capable of the same function, and if no other essential tissue is involved, recovery is possible.

In general, the course is chronic, lasting from one to three or four years from the earliest recognizable symptoms. Longer durations, eight, ten, even twenty years, have been reported. The longest duration seems to occur in uncomplicated tuberculosis of the adrenals. Atrophy of the adrenals usually causes rapidly progressing cases. Remissions and relative improvement occur spontaneously in most chronic cases. The end is either slow and gradual, with death from exhaustion, or sudden, from diarrhœa, vomiting, fever, syncope from exertion, or with toxic symptoms not always possible to explain.

Treatment.—The manifold causes and complex pathology of Addison's disease do not permit a scientific therapy at present. We are obliged to depend upon more or less imperfect theories or an empirical treatment, both of which have been far from satisfactory. The clinical diagnosis can rarely include accurate knowledge either of etiology or of pathological anatomy. On the ground of probabilities we can assume that tuberculosis is the cause in most cases. Sometimes we may make this almost certain by the results of specific tests.

In very rare cases syphilis may be recognized as the cause. Atrophy and some cases of destruction or pressure from tumors will remain as stumbling blocks in practice. Moreover, even in cases with known etiology, we cannot determine the extent of the lesion in the adrenals, the implication of the other chromaffin tissue, the possible compensatory hypertrophy of accessory cortical tissue, or the involvement of sympathetic or spinal nerves.

There is need for more direct examinations of the local conditions. In cases of recognizable tumor an attempt at operation is certainly justified. From the bad prognosis in general, it would seem proper to explore, surgically, in doubtful cases. The difficulties, not to say dangers, of such operations seem at present almost too great to justify them, but with improvements in technique such as can confidently be expected this objection will

not be so strong. Oestreich[1] has made an important contribution to the operative treatment of adrenal disease. A woman with general symptoms, but without bronze skin, had a tumor in the stomach region the size of a small apple. This was extirpated and found to be a tuberculous adrenal. Recovery followed. It does not seem rational, as some have done, to assert that this was not a case of adrenal inadequacy. The symptoms were not complete; the disease was one-sided; compensation might have followed the possible healing of the diseased gland. But to wait for such a process to heal spontaneously would seem almost as absurd as to leave a tuberculous appendix or Fallopian tube to a similar fate.

The spontaneous remissions and the rare cases of recovery have led to a complete denial of the efficacy of treatment. It has been said that cases reported as recovered were only functional. Skepticism is very desirable in such matters, but it must be conceded that we cannot, especially in the early stages, draw the line, and it would be better to assist recovery of a functional inadequacy, if we can, than to follow a purely expectant treatment.

Two plans are available, the so-called causal, and the symptomatic treatment, to which may be added the etiological, applicable in syphilis and tuberculosis.

Adrenal Therapy.—The treatment by adrenal glands or their preparations is sometimes spoken of as "causal" or "substitution" therapy, but obviously with a set of processes very different from those present in the treatment of myxœdema with thyroid preparations. So, we can substitute the faulty or absent secretion of the adrenal medulla with glandular tissue, with other chromaffin tissue, or with adrenin or its congeners. But even if we give cortex tissue or its extracts, we have no assurance that it will replace the function of the live and healthy cortex.

The method is as yet purely experimental. We do not know either the best preparation or the dosage. Various plans have been followed; all have given good results in some cases, and all have failed in a larger number. The active principle of the medulla may be expected to have a good effect upon the muscles, the heart, and probably the pigmentation. Such an effect has been seen in patients treated, and a very striking fact is the relapse that sometimes comes after the cessation of the remedy. In some cases lassitude disappears, the muscular weakness also. In one case (Langlois) ergographic tests showed normal conditions after six weeks' treatment. In some cases the pigmentation subsides rapidly, and returns even more rapidly on stopping treatment. On the other hand, bad results occur sometimes in the very beginning of treatment.

E. W. Adams analyzed 105 cases in 1903, and found that alarming or fatal results had followed in 7, no improvement in 49, improvement in 33, and great improvement ("cures") in 16. Since Adams' report, many more cases have been treated, but without a definite advance in the proportion of good results or in the knowledge of details of treatment. It is impossible to see, at present, any essential difference between the various preparations, but a longer experience may change this.

The fresh glands have been used raw or slightly cooked or dried (Glandulæ suprarenales siccæ, U. S. P.); also liquid extracts. Sheep glands are most commonly selected. Wiesel used chromaffin tissue from calves with

[1] *Zeitschr. f. klin. Med.*, 1897, xxxi, 123.

good results, but the difficulties in obtaining such tissue make this an unimportant source. The dose of gland or extract given has varied considerably, up to six fresh glands a day or 5 to 20 grains of extract three times a day.

Adrenin and similar active principles have been used hypodermically and by the mouth. The latter method is probably just as certain as the former, for as Oliver and Schaefer proved, stomach digestion does not destroy the active principle. A dose of 5 minims of the 1 to 1000 solution can be given three times a day in the beginning, and increased, according to the effect, up to 30 minims. Boinet (1903), who used smaller doses—$\frac{1}{3}$ milligram of adrenalin—warns against large doses, and against treatment in advanced cases. He also thinks the dose should be made smaller as treatment progresses, and the free intervals longer.

All these points should be carefully worked out experimentally, with as complete observation of patients as possible. As an example of the condition now, the blood pressure should be raised by specific glandular treatment. Many observers assert that it is, but some found no rise. That no effect is produced upon metabolism is only to be expected. It has been suggested that as the blood pressure raising action of digitalis resembles that of adrenin, it could just as well be given. To a certain extent this is true, but, on the other hand, digitalis has no advantages over adrenin in Addison's disease and is no freer from untoward effects. The danger of arterial degeneration under adrenin treatment must be borne in mind.

To sum up this part of the subject, the use of adrenal preparations in Addison's disease is legitimate, but they should not be given to the exclusion of symptomatic treatment. They are more promising in the early stages, and must be used with extreme care in advanced cases, but even in the latter are permissible. The preparations must be carefully selected as regards purity. The investigations of Reid Hunt[1] show that there is too much difference in the strength and quality of commercial preparations. No positive lines can be laid down for dosage and frequency of administration. The condition of the patient, and especially the blood pressure, muscular strength, and general sensations, should be carefully observed and used for the direction of further treatment.

The treatment in syphilitic cases needs no special description here. It must follow the known rules. In tuberculous cases, specific treatment with tuberculin preparations might seem indicated, but experience has shown that tuberculin in Addison's disease is very often followed by alarming symptoms. Perhaps the reaction in the vicinity of the affected tissue causes acute functional disturbances. While a cautious use of tuberculin at the hands of one who is accustomed to it, and with all proper care of the patient, is justifiable, it would doubtless be safer to depend upon the general treatment of tuberculosis, on lines now familiar to all. This can be considered with the symptomatic treatment, as the principles are precisely the same.

Symptomatic Treatment.—This is based upon the clinical features of the disease. For the muscular and cardiac weakness, rest is necessary, and should be more or less complete according to the condition. In the most severe stages the patient must not be allowed to raise his head or to exert himself in any way. Prolonged examinations may cause alarming or even

[1] *Journal of the American Medical Association*, September 8, 1906, p. 790.

fatal weakness. The body should be kept warm. The diet should at all times be nutritious and easily digestible. Eggs, milk, toast, soups, gruels, custards, cornstarch and arrow root, junket, buttermilk or fermented milk, or "milk foods" can be used. Meat is usually not craved or well borne. Dilute hydrochloric or tartaric acid may be given.

Gastric symptoms should be looked for, and upon the first indication of indigestion food should be stopped or reduced, according to the severity. If vomiting occurs or seems imminent the stomach should be carefully washed out with hot saline solution. Ice pills, carbonated water, or champagne may then be used, and if there is nausea, or tenderness, an ice bag or a large mustard plaster may be applied to the epigastrium. Grawitz reports two cases "cured" by gastric lavage, and though one may doubt his explanation, the treatment must often be of decided value. Constipation should be guarded against by diet, mild enemas, or the mildest cathartics. Strong purgatives are never admissible, as they may cause fatal collapse. Diarrhœa should be treated by restriction of diet, enemata or colonic flushing carefully used, bismuth, paregoric, or other suitable opiates. Strychnine, arsenic, and other drugs have been used as tonics, and often seem useful. Digitalis may be given in small doses (5 minims of the tincture three times a day). An important aid in all cases is fresh air, due precaution being taken to prevent chilling. Bramwell has reported a case improved at a temperature near the freezing point, and patients may be out-of-doors in much colder weather without obvious harm, but for the outdoor treatment of such a disease very cold weather has serious drawbacks. For the heart weakness and syncope, that are so frequent, hot water bags should be applied over the heart, hot coffee given internally, or subcutaneous injections of strychnine, camphorated oil, or ether used.

CHAPTER XVII.

DISEASES OF THE THYROID GLAND.

By GEORGE DOCK, M.D.

ANATOMY AND PHYSIOLOGY OF THE THYROID.

The thyroid is a ductless gland composed of two lobes lying on each side of the larynx, and joined in most cases (80 to 85 per cent.) by a middle lobe or "isthmus" which crosses at the third and fourth rings of the trachea. The isthmus may be free from the lateral lobes. When it is absent, the lateral lobes lie close together. In front the thyroid is covered by the sternohyoid, sternothyroid, and omohyoid muscles. At the sides it reaches or overlaps the sternocleidomastoid muscle and partly covers the carotid arteries. The recurrent laryngeal nerves lie behind the lateral lobes between the trachea and œsophagus. The lower ends of the lateral lobes extend almost to the level of the sternum, the upper ends to the level of the middle of the thyroid cartilage. The gland is closely united with the larynx and trachea, so that it moves with them, rising in swallowing. The "processus pyramidalis," more accurately described by Lalouette, is a conical body extending up from one or both of the lobes or the isthmus to the thyroid cartilage, hyoid bone, or thyrohyoid membrane. It is not constant, but occurs in one-half to two-thirds of bodies examined, and varies in structure from well-developed glandular tissue to masses of cells resembling accessory thyroid glands. According to Bland Sutton, it represents part of the thyroglossal duct. Accessory thyroid glands occur, but vary in number and place. In general they are most frequent near the hyoid bone, but they occur also on the larynx and trachea and on the aorta. They have the structure of thyroid tissue, sometimes with colloid, sometimes of more embryonic type. They have been much confused with the parathyroid glands. They are chiefly important when they undergo morbid enlargement, and will be mentioned more fully in connection with goitre. They may be supposed to functionate as other thyroid tissue, and to be capable of hypertrophy in order to compensate for loss of thyroid. Part of their supposed protective action we now know is really exerted by the parathyroids.

The blood supply of the thyroid comes from the superior and inferior thyroid arteries and the thyroidea ima (in about 10 per cent. of cases), and is relatively large, the transverse section being about equal to that of the vessels of the brain. The veins form a plexus over the gland and empty into the internal jugulars or brachiocephalic; they are without valves. The lymphatics begin in lymph spaces around the vesicles, form rich anastomoses, and finally pass through the superior and inferior deep cervical glands. The nerves rise from the inferior and middle cervical ganglia. They accompany the blood vessels and end partly on the latter, partly on or between the epithelial cells of the follicles.

The weight of the thyroid varies much according to age, but also according to locality. In the United States, Wells found the weight in persons over forty-five years, 16 grams; between twenty and forty-five years, 25 grams. Thyroids of 50 grams weight or more have been found with normal histological appearance. The gland is larger in women than in men; relatively larger in infants than in adults (1 to 700 to 1000 of body weight compared with 1 to 1500 to 2200). On the average the right lobe is larger than the left. The absolute measurements are, on the average: Transverse, 50 to 60 mm.; length of lateral lobes, 50 mm.; height of isthmus, 5 to 15 mm.; thickness of lateral lobes, 18 to 20 mm.; of the isthmus, 6 to 8 mm.

Development.—The thyroid is derived from the pharyngeal hypoblast, and from masses of cells in the fourth branchial clefts. Fusion takes place about the seventh week. The fetal thyroglossal duct becomes obliterated in the fourth month, the foramen cæcum of the tongue indicating its mouth.

Structure.—The surface is smooth and the consistence soft, but harder in the bloodless organ; the color is reddish brown. The gland is enclosed in a fibrous capsule which sends septa of various sizes into the interior. It is made up of follicles, round, tubular, sacculated, prismatic, or branching, from 15 to 150 microns in diameter. The follicles are lined with columnar or cubical cells, which rest upon the blood and lymph vessels without any membrana propria. Some vesicles are without lumen, others contain the so-called colloid. The size and shape of the follicles and their cells and the amount of colloid vary in different cases, even when there is no evidence of thyroid disease. The cells are described as of two kinds: The "chief cells," the more numerous, are clear or finely granular, without distinct cell membranes. The "colloid cells" are more granular and opaque, the granules staining like colloid. They seem to be derived from the former, so that the two kinds have not such differences as the principal and peptic cells of the stomach. Acidophile granules and fat are found in the cells. Desquamated epithelial cells and also red blood corpuscles, as well as blood pigment, often occur in the colloid. In the latter are also found clear spaces, so-called vacuoles. These are thought by some to be artefacts, by others to be albuminous material in the colloid. It is not known whether the colloid is secreted as such into the follicles, or formed partly by secretion, partly by degenerated cells (Huerthle). There is little doubt that it becomes altered in the follicles. The differences in composition give different histological pictures. If thin, it stains less intensely in general, and better with eosin or picric acid than with hematoxylin or acid fuchsin. If very thin, fixing solutions produce granular appearances, or fibrils or meshworks, that cannot be produced by the same methods in all thyroids, and so are not wholly artefacts. In the septa lie the blood and lymphatic vessels and nerves. The lymphatics are noteworthy because they often contain colloid material or a substance with similar optical and staining qualities. The colloid enters the general circulation either through the lymph spaces around the follicles, or the lymphatic or bloodvessels, perhaps also by rupture of intervesicular walls, by which the lymphatics are also ruptured. Several observers, such as L. R. Mueller, von Ebner, and de Quervain, could not see evidence of such passages. Between the follicles epithelial cells can often be found singly or in groups. They are sometimes supposed to be embryonic remains, but they do not seem capable of taking up active development on extirpation of part of the gland.

Chemistry.—The most important chemical feature of the thyroid at present is the iodine content of the colloid material, discovered by Baumann in 1895. The iodine exists in an organic compound, "iodothyrin," or "thyroiodin," in which iodine is present in proportions of 9 per cent. or more (14.29, according to Oswald). The actual amount of iodine in a single gland varies from 2 to 9 mg. The iodothyrin in turn is combined with a proteid called "thyrogen" by Blum. Oswald showed that colloid contains a mixture of albuminous bodies, and he distinguishes the iodine-containing "thyroglobulin" and a nucleoproteid, thyro-albumin, free from iodine, but rich in phosphorus. There are remarkable differences in the amount of iodothyrin present in thyroids of different kinds. It is absent or present only in very small amounts in the newborn, and also in some animals, such as foxes and some other wild-living carnivora. It varies remarkably in total amount in thyroids in different parts of the world, but is relatively and absolutely less in goitrous districts. In goitrous colloid the amount is small and the total iodine much less than that of normal thyroids, *e. g.*, 2.5 mg. as compared with 10 or 12. In non-colloid goitres iodine may still be present.[1] It is diminished in general disease and in menstruation; it is stored up in the body during pregnancy.

Function.—Our knowledge of the function of the thyroid began with the observations of Gull (1873) and Ord (1878) on the disease now known as myxœdema, and the observations of Kocher and Reverdin (1882, 1883) on cachexia thyropriva or cachexia strumipriva. Up to that time many held theories no stronger than that of Wharton—that the thyroid was for the purpose of giving the neck a beautiful shape, although Schiff had made experiments in 1859 indicating some of the features since then demonstrated by various observers, and in 1884 put the modern theory on a firm basis. Many of the results of experiments are vitiated by ignorance of the existence and function of the parathyroid glands. The following statements, however, will probably stand the test of future experiments.

The thyroids are essential to life. If they are wholly removed, death occurs with cachectic symptoms. If part (one-sixth, Beresofsky) of the gland is left in situ or transplanted into another part of the body, or if accessory thyroids capable of hypertrophy are left behind, or if thyroid substance or its active principle be ingested, the consequences of removal will be less severe, or may be escaped entirely. Such regeneration, or compensation, for probably both are concerned, is more likely to occur in young animals, as shown by Wagner, Horsley, Breisacher, and others.

Two opposite sets of symptoms follow from diminished and excessive thyroid activity respectively. With diminution, growth is lessened. In the young animal not only is macroscopic growth diminished, but cells fail to reach their proper development and the connective tissue remains myxomatous. The skin and hair show impaired growth. The nervous system undergoes degeneration and its function is impaired, as shown by psychic, motor, and sensory disturbances. The heat regulation, metabolism, and gaseous interchange are all depressed. The results of lessened activity of thyroid function will be more fully dealt with in connection with myxœdema and cretinism. Excessive activity of thyroid function, produced experimentally by feeding with suitable preparations, is shown by excessive

[1] See Marine, *Johns Hopkins Hospital Bulletin*, September, 1907, p. 359.

metabolism, decrease of weight, not only from destruction of fat, but also of proteids, increased growth of long bones in young animals, and various nervous symptoms, affecting the heart (palpitation and tachycardia), the central nervous system (irritability, sleeplessness), and the peripheral nerves and muscles. Glycosuria is not rare. These conditions will be discussed in detail in connection with Graves' disease.

There are various theories of thyroid function, theories that are often opposed to each other, yet fuller knowledge may show that both contain elements of truth. One of the most prominent is that the thyroid secretes a substance necessary to normal metabolism, another is that the secretion neutralizes poisonous substances produced in the body either in the gland itself or in the body outside of the gland. With the discovery of iodothyrin it was supposed that a long step had been taken in explaining the function of the gland, and that the thyroid function would soon be made clear. Further research has encountered fresh difficulties, although actual knowledge is more accurate than before. Some data may with advantage be stated before taking up the details of thyroid diseases.

The Colloid Matter.—It has been mentioned that our knowledge of the formation of colloid is incomplete. More than that, there are no infallible microchemical or fixing and staining methods by which we can recognize colloid. It is also unsettled how the colloid leaves the thyroid, but that it does leave the gland there can be no doubt.

As regards the iodine, we now know that iodine is not restricted, in the body, to the thyroid. This is not remarkable, seeing how widespread an element it is, occurring everywhere; more so near the sea than inland; less on mountains than on plains. It occurs in many plants and animals. According to Bourcet, $\frac{1}{3}$ mg. is ingested daily by human beings, in food. In man it is found in all the organs, especially the thyroid of adults, the adrenals, muscles, parathyroid, hypophysis, central nervous system, thymus, spleen, lymph glands, liver, and kidney. It has been found in cell nuclei. In all other organs it is always in very much smaller amounts than in thyroid. In hair and muscle the amount increases with the ingestion of iodine. In the thyroidectomized dog iodine can still be found.

We have no way of recognizing either the richness in iodine or the amount of colloid during life except by its effects, and the experimental findings are very contradictory at present. Full vesicles and colloid in lymphatics (or in veins or arteries) are not proof of active secretion. In the newborn there is little or none, and although it may be said the function has not yet developed, the thyroid of Graves' disease also contains little, although a hyperfunction is generally admitted. It is obvious that storage, on the one hand, and rapid exit, on the other, may account for some of the discrepancies. In Graves' disease the rapid flow of blood through the gland may assist in keeping the latter relatively empty. A similar explanation can be made for acute infections, in which, as autopsies show, the vesicles are also often found empty. Thick colloid is probably evidence of long stay in the gland, but we do not know whether such colloid is either more or less concentrated as regards its essential constituents. A. Kocher has shown that some non-functionating goitres may be full of colloid. In short, the presence or absence of colloid is no criterion of the intensity of thyroid function. The latter may be supposed to depend rather upon the amount of production and the rapidity with which the secretion leaves the gland.

Lücke has shown that the activity of secretion is governed by the nerves. It is uncertain whether thyroid secretion is continuous or periodic, but the latter seems more probable.

In cases with little colloid and rapid blood flow, it is probable the latter is primary as regards the thyroid, although the cause of the rapid flow may be due to some distant nervous reflex or chemotactic influence. The rapid disappearance of colloid in transplanted organs can readily be explained by the active circulation in such cases.

The true nature of "iodism" and "thyroidism" have not yet been cleared up by the numerous investigations of thyroid functions and of iodine in the body. Iodine in other forms does not act like thyroglobulin in oxygen and nitrogen metabolism in health, or in obesity and myxœdema. "Iodism," so-called, as Lebert suspected, is more likely a thyroid intoxication, and will be mentioned more in detail in connection with goitre. Very recently Reid Hunt has made some important investigations in regard to the thyroid secretions. Roos thought there was a relation between the amount of iodine and the physiological activity of the thyroid. Oswald thought iodine essential to the activity of the thyroglobulin. Hunt asserts: (1) That the physiological activity of thyroid, as tested by poisoning by acetonitrile and morphine, varies directly with the percentage of iodine. (2) Iodine-free thyroid has a low degree of physiological activity. (3) This can be increased by adding iodine to it, or by taking up iodine in the body.

As Hunt says: "It seems possible that a thyroid may be ineffective either by producing too little of the normal iodothyroglobulin, or by producing a thyroglobulin too poor in iodine. It also seems possible that the thyroid may meet increased demands in various ways: by an increase in the percentage of iodine, by an increase in the iodine-free constituents, or, most advantageously, by an increase of both. In addition, it may be supposed that in some conditions there is a more rapid circulation of iodine." Kraus points out that the results in Hunt's experiments may be due to the increased metabolism induced by the thyroid secretion, setting more sulphur free to combine with the toxic substance. It is very doubtful whether thyroglobulin represents all the active substances of the thyroid, even if we believe it the most important in many respects.

Other Relations of the Thyroid Gland.—Its close relation with the reproductive organs is shown by the (congestive) enlargement in menstruation and pregnancy; the greater demand for thyroid secretion during pregnancy, as shown experimentally by Halsted; bitches with partial thyroidectomy, free from symptoms, gave signs of athyrosis while pregnant and recovered after littering. It is possible the thyroid enlarges in pregnancy in order to supply the fetus, which does not yet contain iodine in its thyroid. That there is a relation between the thyroid and the kidneys is believed as the result of certain observations in eclampsia. Blum observed nephritis in thyroidectomized dogs. The atrophy of the thyroid in old age may be the result of the decline of the sexual life. The thyroid arteries are said to become sclerosed relatively early.

The red blood corpuscles decrease after thyroidectomy. This is not now looked upon as evidence of blood forming powers on the part of the thyroid, but rather as the result of increased destruction of blood by toxic substances no longer neutralized, or of deficiency of the activity of the blood-forming organs from one or the other effect.

The experiments, in regard to cytolytic or cytotoxic thyroid serum, of Mankovsky, Gontscharukof, Yates, MacCallum, and Portis need not be detailed here,[1] although they promise further additions to our knowledge of thyroid physiology.

The parathyroid glands have such close anatomical relations with the thyroid, and their pathological relations have been thought to be so intimately combined, that it seems well to devote some attention to the parathyroids before discussing diseases of the thyroid gland.

THE PARATHYROID GLANDS.

It is not yet possible to describe diseases of the parathyroid glands according to a scientific classification, nor even according to a clinical arrangement such as long experience has furnished for diseases of the thyroid gland. It therefore seems best to summarize the most important data in such a way as may furnish a useful base for further advances.

Nomenclature.—Parathyroid glands; glandulæ parathyreoideæ (Latin); glandules parathyroidiennes (French); Beischilddrüsen (German); Ghiandole paratiroidee (Italian). Various other names have been proposed, such as Nebenschilddrüsen (Hofmeister, 1892), accessorische Schilddrüsen (Zielinska, 1894), glandules thymiques (Torneaux and Verdun, 1897), glandules branchiales (Verdun). Following A. Kohn's suggestion, many writers, especially in Germany, have used the term "epithelial bodies." While "parathyroid" is inconvenient in suggesting thyroid functional relations, it has the advantage of priority, and in English literature seems too well established to be changed. It is incorrect to apply the term "epithelial bodies" to the parathyroids specifically. Von Verebély's name, "branchial epithelial bodies," is more accurate, but awkward. The same criticism may be made of the terms "parathymus" and "parathyroid" for the two pairs of parathyroid glands. It would be better, perhaps, to follow Verdun's suggestion and speak of them as branchial glands (glandules branchiales) with the Roman numeral III or IV to signify the branchial cleft in which the gland originated and hence its position.

Historical.—The development of our knowledge of the parathyroids has followed a devious course. Anatomical, physiological, clinical, and pathological discoveries have each influenced the others. A chronological order will best serve to set forth the most important steps.

The parathyroids were doubtless seen and partially described by earlier observers, notably Remak (1855) and Virchow (1863), but the first one to describe them specifically was the Swedish anatomist Sandström, who discovered one pair of these glands in 1880. Berger, who made a full abstract of the paper for *Schmidt's Jahrbücher*, should not be forgotten in this connection. Sandström thought the bodies were embryonic thyroid tissue in various stages of development, although he also recognized their resemblance to the pituitary body. Baber and Woelfler independently and about the same time described the bodies, but did not make clear their distinction from the interfollicular cells or undeveloped portions of the thyroid gland. Baber, in fact, spoke of the bodies as "undeveloped portions." Sandström left

[1] Milton M. Portis, *Journal of Infectious Diseases*, January, 1904, i, 127 to 139.

unsettled the possible physiological function of the bodies. He thought they might be important as the sources of morbid conditions in the neck, just as the accessory thyroid glands were.

Practically nothing was added to our knowledge of the bodies, nor were they often mentioned, until (1891) Gley re-discovered them, found they had been described by Sandström, and began a notable series of experiments to determine their function and their place in pathology. He, like Sandström, knew of only two parathyroids, the lower or "external" pair. Gley saw in them the explanation of the symptoms that sometimes follow thyroidectomy or strumectomy—the cachexia thyropriva or strumipriva, characterized by myxœdematous or cretinous conditions, and tetany. By removing the thyroid with or without the external parathyroid bodies he was able to produce or to avoid tetany. He therefore thought the parathyroids could compensate for the extirpated thyroid by differentiating into thyroid tissue. This belief was strengthened by finding, as he thought, hypertrophy in the parathyroids left in the body. These experiments, erroneous as the conclusions drawn from them were, had two important results. They gave an explanation for the difference in the results of thyroidectomy in carnivora and herbivora—the escape of the latter from fatal tetany being due to the greater ease of leaving undisturbed (two of) the parathyroids. Much more important, they stimulated numerous investigators to attack various problems relating to the parathyroids.

It was soon discovered (Cristiani, 1892 to 1893) that the parathyroids were sometimes embedded in the thyroid, and that some animals (bats, Nicolas, 1893) had four. Embryological studies by Prenant (1894) began to indicate the independent character of the bodies. This was made more certain by A. Kohn (1895), who showed that there were, as a rule, four parathyroids in various kinds of animals, distinguished between the accessory thyroid glands and the parathyroids, and identified these bodies with the "epithelial bodies" described by Maurer (1887) in amphibia. The advocates of the thyroid nature of the parathyroids continued to urge the older view, and their work had the beneficial effect of stimulating the other side to more careful and accurate experiments. Hofmeister proved that the bodies do not undergo compensatory hypertrophy after thyroidectomy. Such an enlargement, if it occurs, can be explained by the effects of the operation on the bodies themselves. Moussu (1897) asserted that thyroids and parathyroids have distinct functions, the loss of the former causing trophic disturbances, myxœdema, cachexia, or in young animals cretinism, the total extirpation of the parathyroids producing rapidly fatal convulsions. The partial loss of the parathyroids he thought caused symptoms suggesting Graves' disease. These ideas, especially the latter, continued to attract attention longer than they deserved, for it was shown by others that trophic disturbances also follow parathyroidectomy, and the relation to Graves' disease was shown, especially by MacCallum, to be unfounded both clinically and anatomically. Observations and experiments of Biedl, Leischner, Lusena, Cristiani, Alquier, Welsh, and especially Vassale and Generali (1896), made it certain that there was a causal relation between extirpation of the parathyroids and the convulsive attacks well known to certain thyroid operators as postoperative tetany. It was known that tetany never followed the extirpation of a lingual thyroid; it was shown that the severity of tetany was in proportion to the amount of parathyroid removed, and that temporary tetany could be pro-

duced by interference with the blood supply of the parathyroids. "Tetania thyropriva" became "tetania parathyropriva," with results speedily recognized by most surgeons. Jeandelize, Biedl, and Paltauf completed the demonstration of the difference between the chronic, trophic, thyroid symptoms and the acute, convulsive, parathyroid symptoms.

Anatomy.—Before entering into the pathological relations of the parathyroids, it will be well to describe their normal anatomy and relations. The latter are especially important to surgeons and to those who may have opportunities for postmortem studies.

Number.—According to W. G. MacCallum,[1] "four may be regarded as the normal number" in man as in lower animals. "Doubtless there occur anomalous cases in which only two or three glands exist; but in many of these instances, if not in all, the remaining glands have increased correspondingly in bulk, and it seems probable that in most of the instances in which four glands cannot be found this result is due not to a real deficiency in the amount of parathyroid tissue, but to lack of energy and patience in the search for the rest of the glands." "Sometimes they are very conspicuous from their size and peculiar color." "It is particularly difficult to come upon them in very obese persons, and difficult to recognize them in those individuals in whom some wasting disease has caused the fat to atrophy into brownish, isolated masses which may be easily confused with the gland, or when the field is discolored by blood." "There is usually no great difficulty in recognizing them when they are seen, nor in distinguishing them from other bodies of the same size which may lie near, such as accessory thyroid lobules, bits of thymus tissue, lymph glands, or hæmolymph glands." Many, however, find the bodies hard to recognize at operations.

Physical Characteristics.—The average size of the parathyroids is about 6 to 8 by 3 by 1 to 2 mm. Some are as large as 1 cm. by 4 to 5 mm., others much smaller. "They are flattened and usually elliptical or tongue-shaped, and quite soft. This soft, flabby consistency aids greatly in distinguishing them from bits of thyroid tissue, which are much more firm and elastic, or from lymph glands, which are also much firmer. Their surface is always quite smooth and glistening, and except for the red lines of minute vessels, it is homogeneous in appearance, differing in that respect from the grayish pink or red lymph glands, in the surface of which the opaque lymph cords can generally be made out as whitish gray dots. In color they are of a clear light brown, which may be rendered pale by anæmia and the accumulation of fat, or converted into a brownish red by congestion. It is particularly this bright brown color, together with their flabby softness, which makes them easily recognizable" (MacCallum).

Location.—The glands lie along the posterior inner edges of the lateral lobes of the thyroid, as a rule, but there are many variations. "It is often difficult or impossible to find both of them on each side; one or more may lie on the lateral aspect of the thyroid or even upon the part of the trachea below the thyroid as far as the bifurcation." "The recurrent laryngeal nerves, which have been suggested by certain surgeons as a guide to their position, run in a general way in the region where they are most commonly situated, but the glands bear no definite relation to them, and frequently lie far away from the line of their course."

[1] *British Medical Journal*, 1906, ii, 1282.

MacCallum finds that the terms "inner," or "internal," and "outer," or "external," used with reference to the parathyroids in lower animals, are not so applicable in man as "upper" and "lower." "In most instances the lower and larger glands lie near the posterior edges of the thyroid lobes in the loose tissue which fills the notches just above the rounded lower lobules, and among the branches of the inferior thyroid arteries which enter the thyroid at those points. In most cases the upper glands lie against the œsophagus, at the points where the superior thyroid arteries fade away along the posterior edges of the thyroid lobes."

In man MacCallum did not find any of the glands embedded in the thyroid, as occurs commonly in the dog. The more minute details of this part of the subject are important to the surgeon, but do not interest so much the physician or the prosector.

Accessory parathyroid glands occur and are frequent in animals. In a rabbit Erdheim found nine. The importance of such glands in anomalous cases need not be emphasized, but must be considered just as carefully as the probability of a smaller number than four, especially in cases demanding surgical operations with the possibility of removing or injuring one or more of the glands.

Embryology.—The parathyroids are generally believed to be derived from the epithelium in the third and fourth branchial clefts, very close to the lateral thyroid anlagen.

Structure.—The glands have a fibrous capsule which sends thin strands into the substance of the organs. The parenchyma is made up of epithelial cells with large nuclei, filling the meshes of the rich capillary network, and often arranged in branching beams. Along the stroma the cells are sometimes arranged in rows—"palisade" or "balcony cells." The cells were classified by Welsh as "principal" and "oxyphile" (acidophile, eosinophilous). The difference is probably due to various stages of functional activity. Glycogen is often present in the cells, and has been considered a product of parathyroid secretion.

From the time of Sandström various observers have noted clear spaces, cavities, or cysts, and sometimes a glistening fluid like colloid, although it is no longer believed, as formerly by some, that this is the same as thyroid colloid. Exchange between the cells and the blood is favored by the wide vessels lying with their endothelium directly on the cells. The capillaries are wide, of the type called "sinusoid" by Minot. Ginsburg (1908) has shown the existence of an anastomosis between the parathyroid arteries of the two sides. The parathyroid glands are ductless glands or blood-vascular glands of the most typical kind. They resemble many other small ductless glands, especially those now classed as epithelial bodies, including the epithelial part of the pituitary body, the cortex of the adrenals, and the islands of Langerhans. According to Kohn, the carotid gland and the coccygeal gland do not belong among the epithelial bodies.

Results of Parathyroid Lesions.—As we have no direct knowledge of the secretion of the parathyroids, it is necessary to get as clear an idea as possible of the functions of the organs by the method of experiment and by observation in case of disease.

The most striking and, so far as we know now, most serious result of parathyroid lesion is *tetany*. It would be more accurate to say postoperative tetany, for tetany is most clearly associated with the destruction or extirpa-

tion of the parathyroid bodies. In animals, as the result of design or accident, the sequence is now well known. In man, the relations have been established by several observers, especially Benjamins, von Eiselsberg, and Erdheim. (The divergent views of some authors, especially Vincent[1] and Jolly, D. Forsyth,[2] Kishi, Blumreich and Jacobi, and Blum and Caro do not seem necessary to set forth in detail.) MacCallum, Halsted, Pineles, and others have supposed that tetany could occur from pressure of a goitre upon the parathyroids. This has been questioned by many, and it is, indeed, difficult to understand why, if it can occur, it is not more frequent.

The tetany following total removal of the parathyroids, or their destruction by cutting off the circulation, comes on in from two to five days after operation. In some cases, in which the causes are obscure, but doubtless related to the circulation in the parathyroids, symptoms come on months after operations in the vicinity of the glands. The symptom complex is characterized by convulsions, spasmodic contractions with "accoucheur's hand," rapid and labored respiration, and salivation, with death in a short time, or sometimes after a period of a few days, with stupor or coma. The temperature is not much elevated; the heart's action not markedly accelerated.

The symptoms that follow incomplete extirpation or temporary interference with the nutrition and function of the parathyroids resemble those described, but are milder and usually transitory. Halsted has termed it "subtetanic hypoparathyrosis," and has given a vivid description of a case.[3]

Non-operative Tetany.—The close resemblance of operative tetany to the form so often observed clinically early led various investigators (Jeandelize, Pineles, MacCallum, and others) to the view that the so-called idiopathic tetany is also due to parathyroid disease. Chvostek accepts the general identity of all forms of tetany. He points out that the variability of the clinical phenomena, the differences in intensity, and the negative anatomical findings suggest a functional disease, while the characteristics of the convulsions, usually so typical, and the mechanical and electrical changes in the muscles and nerves, oppose the idea of a purely functional disease, so that tetany occupies a position between organic nervous disease and functional disease. The typical clinical picture, Chvostek shows, might originate in one of two ways: through the action of a specific poison, or through the existence of a specific reaction which leads to tetany in some persons following injuries or irritants that do not produce tetany in others. The specific tetany reaction he ascribes to a functional disturbance of the parathyroid bodies. This can be congenital (as in the family tetany) or acquired. It does not necessarily induce symptoms until the exciting cause comes into play. The latter may be such a thing as a circulatory disturbance in the head, as in cobblers' work, or in retching from vomiting or gastric lavage. Chvostek also points to the endemic relations of tetany, its seeming antagonism to goitre, and its seasonal occurrence, as proof of such a relation as he claims to exist between tetany and the parathyroids, and he looks upon the facial phenomenon as an easily demonstrable and important symptom of parathyroid disease, "a reagent which indicates a functional disturbance of those organs." In order to strengthen his view that the organic disposition

[1] *Lancet*, 1906, ii, 348, 430.
[2] *British Medical Journal*, 1907, ii, 1508.
[3] *American Journal of the Medical Sciences*, July, 1907.

is more important than the exciting cause, Chvostek injected tuberculin into persons who had recovered from tetany, or had imperfect cases, and in six cases was able to call forth tetanic phenomena.

MacCallum has made many careful and ingenious experiments to clear up the pathology of tetany. His results indicate the existence, in animals deprived of the parathyroids, of a poison which combines with certain cells in the central nervous system. The same theory can be applied to non-operative tetany. It would seem that these poisons, whether produced within the body or absorbed from without, are normally neutralized by the parathyroids. By bleeding an animal with tetany, or by washing it out with salt solution, the appearance of tetany symptoms may be checked for some days. The symptoms can also be made to disappear by injecting emulsions of parathyroids, and this can even be done a second time in the same animal. Carbohydrate diet, and also milk, has a slight effect upon the appearance of the symptoms, but the latter can occur even in starving animals. MacCallum was not able to produce distinct symptoms by transfusing the blood serum of tetany animals into others. He thinks that either the amount of poison is too small, or the poison rapidly combines with the nerve cells. That the action is upon the latter, and not upon the muscles, MacCallum proved by cutting the muscles free from their nervous connections, confirming earlier experiments of Lanz.

Owing to the nature of the disease, postmortem examinations in subjects of non-operative tetany are at present scanty. MacCallum found in a fatal case of gastric tetany an increased number of eosinophilous cells and many mitoses in the principal cells of the parathyroids. He looked upon these as evidences of hyperplasia, following functional insufficiency of the bodies. Erdheim found the bodies normal in two cases of gastric tetany and one of tetany in a case of cerebellar cyst. Koenigstein found an excess of a glycogen-like body in the parathyroids of one case.

Among other non-operative forms of tetany, that of pregnancy has interesting relations with certain animal experiments on the parathyroids. Vassale and Generali pointed out that animals with mild tetany from partial parathyroidectomy get severe tetany during and after pregnancy. This agrees with earlier observations of Lanz and also Halsted, in which the parathyroids were doubtless involved, although not specifically mentioned. Menstruation, as well as pregnancy, may excite spasms in women with hypoparathyrosis. The alteration of the calcium metabolism, mentioned below, doubtless has a close relation to these facts.

Infantile Tetany.—The study of this condition has added a good deal to the pathology of the parathyroids. Erdheim found hemorrhages or their results in the parathyroids in three cases of infantile tetany, without other lesions of the glands. He thought the hemorrhages might have led to functional disturbances. Koenigstein made a similar observation, but the relation of the lesions was questioned by many clinicians, including Kassowitz, who denied the importance of parathyroid insufficiency in tetany of infants. Escherich was at first in doubt, but recently (1907) he has come to accept the parathyroid origin of infantile tetany. Escherich distinguishes tetany of children, a condition with spasm of the muscles and the glottis and general convulsions, and "tetanoid," in which there is mechanical and galvanic overexcitability without Trousseau's sign and muscular spasm. He bases his belief partly upon the observations of Yanase, who found 38 with hemor-

rhages of the parathyroids among 89 cases of all kinds. In all the cases with positive findings there were records of characteristic electric reactions or convulsions, and a direct relation between the severity of the symptoms and the anatomical changes, but the latter Escherich does not think necessary for functional disturbance. Hypoplasia could suffice, and would be likely to have hereditary features. "Such a condition could account for chronic cases, and compensation could occur later, as in the case of the pancreatic function." Iselin has shown that the offspring of animals deprived of parathyroids have exaggerated electrical reactions, and get severe post-operative tetany with great rapidity.

The treatment of postoperative tetany is largely a preventive one, for the treatment of the condition after it develops, except in very mild and transitory cases, up to the present has been far from satisfactory. If the removal is discovered at operation, the parathyroid should be grafted at once (Halsted, 1908). Von Eiselsberg[1] has grafted a parathyroid into the rectus muscle in a postoperative case of tetany with great success. In animal experiments various methods of treatment have been used, such as the internal and subcutaneous administration of parathyroid tissue, extracts or emulsions, and the transplantation of living glands in various parts of the body. In most cases in which the observations were made with the necessary care, so as to avoid error in the experiment, the results have been disappointing. Halsted and MacCallum, in a human case, used dried and fresh beeves' parathyroids, "with marvellous and almost instantaneous effect at first." "Large doses were given at first, six dried glands every three hours;" later, fresh glands. "The dried glands seemed less effective than the fresh." In this case there was probably cachexia thyropriva besides the parathyroid symptoms. Branham used injections of parathyroid emulsion with great success in a case of accidental removal. After two injections the remaining glands resumed their function. Beebe is experimenting with a parathyroid-nucleoproteid, the outcome of which will be awaited with interest. It or some other organic preparation should be used in the non-operative tetanies, in order to learn whether anything approaching thyroid therapy in cretinism, myxœdema, and other thyroid trophic disorders can be obtained.

The prospects for and technique of parathyroid transplantation are well described by Halsted,[2] whose articles can be consulted for other interesting clinical and operative details. From the experiments of MacCallum and Voegtlin it becomes imperative to put all patients with tetany upon treatment with some calcium salt, as the lactate or acetate.

Other convulsive diseases have been thought to have parathyroid relations besides tetany, especially epilepsy (Jeandelize, Vassale), paralysis agitans (Berkeley), myoclonus, and myotonia (Lundborg). Erdheim, however, has thrown doubt upon the relation of epilepsy, as well as paralysis agitans. R. L. Thompson found the organs negative in nine cases of paralysis agitans. Eclampsia has also been thought to have some relation to the parathyroids, and some interesting observations have been made by Pepere and Zanfrognini, but their evidence is weakened by the contradictory findings of Erdheim.

Trophic disturbances from disease of the parathyroids have been shown

[1] *Deut. Chir. Congr.*, 1908.
[2] *Proceedings of the Pathological Society of Philadelphia*, 1908, Nos. 4 and 5.

to be possible by the experimental work of Erdheim.[1] His observations are especially interesting in view of the investigations by Stoeltzner[2] and Quest[3] upon lime metabolism in tetany. MacCallum and Voegtlin have followed up this line of investigation with important results, showing that "the parathyroids exercise some sort of control over the calcium metabolism." It had been discovered by previous observers that "animals fed on calcium rich milk do not develop tetany so readily as those otherwise fed." MacCallum and Voegtlin "found that in dogs, in which after parathyroidectomy the most violent tetany had developed," "all the symptoms can be instantly dispelled by the injection of a solution of a calcium salt into the jugular vein." The effect "lasts for a day or so, when tetany again appears, and may be cured again by a similar dose." Subcutaneous injection, or solutions by the mouth, act equally well, but more slowly. Investigations of the urine and fæces show that there is an increased output of calcium in the urine in tetany, and the blood contains only about half the normal.[4]

R. L. Thompson has found degenerative or sclerotic processes in the parathyroids in primary infantile atrophy, such as are also found in the thymus and other glands. He does not emphasize the causal relations of the degenerations, but gives a laudable example of the kind of investigations needed.

A relation between parathyroid disease and osteomalacia and rickets has been assumed, but the anatomical evidences are contradictory. Observations upon the organic metabolism in cases of parathyroidectomy show that the relations may not be very important, but the observations mentioned above indicate that the mineral metabolism is very important. In this connection it may be mentioned that MacCallum's efforts to get a specific cytotoxin were unsuccessful. Gley, and also Mendel, found iodine in the parathyroid, but Estes and Cecil point out that the quantity is small.

An antagonism between the function of the thyroid and parathyroid glands has been assumed by some, and the experiments of Eppinger, Falta, and Rudinger suggest antagonistic effects of the two organs on the sympathetic nerves and the blood pressure raising functions of the adrenals. Lusena thought tetany was more severe in animals in which the parathyroids had been removed alone than in those in which the complete operation was done, and also that tetany after removal of the parathyroids alone was checked by subsequent removal of the thyroid. It seems more natural to explain this, if it occurs, as Vassale and Generali did, on the ground of lessened metabolism, and therefore lessened production of toxic material. MacCallum was not able to confirm Lusena's observations. Edmunds, and also Vassale and Generali, found the thyroid colloid disappeared after parathyroidectomy. This might indicate increased functional activity.

A relation between the kidneys and the parathyroids has been supposed by some (Massaglia, Quadi, Manca). In MacCallum's case of parathyroid adenoma, cited below, there was renal insufficiency, "which had existed so long that extra demands might have been made upon the parathyroid."

[1] *Mitth. a. d. Grenzgeb. der Med. u. Chir.*, 1906, Band xvi.
[2] *Jahr. f. Kinder.*, 1906, xiii.
[3] *Wien. klin. Woch.*, 1906, p. 830.
[4] *Johns Hopkins Hospital Bulletin*, 1908, p. 91, and *Proceedings of the Pathological Society of Philadelphia*, 1908, Nos. 4 and 5; *American Journal of the Medical Sciences*, October, 1907.

In two other cases of chronic nephritis MacCallum found signs of parathyroid activity in one but not in the other.

Tumors of the parathyroids have been observed, first by De Santi, later by Benjamins, Erdheim, Askanazy, Hulst, MacCallum, Weichselbaum, von Verebély, and J. Chalmers Da Costa. In several of these the change was apparently benign adenoma of moderate size, although in Benjamin's case the tumor was the size of a child's head. In Erdheim's case the mass was 2.5 by 1.5 cm. As no other parathyroids were found in the (autopsy) body, Erdheim thought the tumor had begun from the stimulus of a functional hypertrophy. In Hulst's case the tumor measured 2.5 by 2 cm.; in MacCallum's, 2 cm. Two normal parathyroids were found in the latter. MacCallum[1] found no colloid, as some others did. He suggests calling the growth adenoma, although recognizing that some so-called adenomata of glandular organs have proved to be compensatory or regenerative.

Of other alterations that have been observed in the parathyroids may be mentioned cloudy swelling, cysts, fatty degeneration, "colloid" change, etc., as well as tuberculosis, but the cases reported are few, and the associated clinical features too insufficiently described to serve as guides to the normal or pathological functions of the glands.

The use of parathyroid in conditions due to their insufficiency has been mentioned. Experiments with the administration of the glands in other diseases, such as myxœdema, paralysis agitans, Graves' disease, eclampsia, epilepsy, and psychoses, in the present state of our knowledge of the subject, are not strongly indicated. So far they have been disappointing.

CONGESTION OF THE THYROID GLAND.

The large size of the thyroid vessels, their rich anastomoses, and the rapid flow of the blood through them, all tend to produce changes in the amount of blood in the gland at various times. This means, of course, that congestion is easily brought about, but it is important to remember that this is not merely such a congestion as may occur in any gland, from secretory stimuli, but has certain peculiarities. Ewald well speaks of the thyroid as a cavernous organ, a view held by Graves.

The tendency of the thyroid to swell in some persons, from emotional excitement, from posture during sleep, from the wearing of tight collars, during epileptic fits, from carrying loads on the head, from forcible expiration, from holding the breath, long since caused the thyroid to be looked upon as a safety reservoir for the brain. The popular and scientific literature on congestion of the thyroid from irritation of the sexual organs—more accurately speaking, the female sexual organs—is enormous, but by no means complete. Menstruation, coitus (especially defloration), masturbation, pregnancy, and confinement have all been observed to be associated with a temporary swelling of the thyroid. It is not known, however, whether this is a mere congestion or whether there is, in some of the cases, hyperplasia or hypersecretion, with temporary excess of colloid in the gland. Forneris reported an increase of 3 cm. during sleep, subsiding in a quarter of an hour upon waking, which could hardly be explained otherwise than by congestion, but the same explanation cannot be accepted for all the other cases.

[1] *Johns Hopkins Hospital Bulletin*, 1905, xvi, 87.

Congestion is often more conspicuous in the goitrous thyroid than in the normal, and although it has been supposed at times that some goitrous enlargements were purely vascular, this is no longer believed. However, even a small goitre, especially in Graves' disease, may have an excessive development of vascular tissue, so that this element predominates on physical examination. While there are reasons for believing that congestion of the thyroid favors the development of goitres, a rapidly developed swelling of the gland, sometimes assumed to be congestive, is often the actual beginning of a goitre. In many cases, also, a condition thought to be congestion of the thyroid may be the congestion with other changes of an inflamed or degenerated gland, as described below.

On account of the facts just stated a diagnosis of congestion of the thyroid should only be made with the greatest reserve, and cases suspected to be of that kind should be carefully followed up with reference to the possibility of inflammation, goitre, Graves' disease, or malignant disease.

Congestion of a normal gland from temporary causes is usually not a matter for *treatment.* If it occurs often, the causal factor should be ascertained if possible. Congestion associated with infection, intoxication, traumatism, or inflammation should be treated as part of the chief condition.

THE EFFECTS OF TOXIC AND INFECTIOUS PROCESSES IN THE THYROID.

Thyroiditis.—Historical.—Under various names, such as cynanche or angina thyroidea, thyrophyma acuta, struma inflammatoria, thyro-adenitis, conditions have, from time to time, been described that were supposed to represent inflammation of the normal or goitrous thyroid. In some cases, as in the use of the French term "thyroidite," the two conditions were voluntarily included. There are good reasons, scientific as well as practical, for considering together inflammations of the normal thyroid and of goitre, but it is preferable to speak more fully of the former in this place, and to consider the latter as a complication of goitre. According to custom, under normal thyroids in this section some organs are included which show a slight diffuse hyperplasia. While these are in a sense goitres, they often react toward irritants more like normal glands than do larger, and especially nodular, goitres.

Accurate knowledge of the inflammations of the thyroid is comparatively recent. It began with Bauchet (1857), was enlarged by Lebert (1862), and became much enriched but also confused in the years following the early investigations in thyroid disease. Lücke made an important study in 1874, but it was not until a much later period that positive advances were signalized by the investigations of Basso (1892), Jeanselme (1895), and Mygind (1895). Mygind's work was especially weighty, because he emphasized the importance of simple thyroiditis as against the more obvious suppurative or gangrenous forms. He was followed by Sokolow, Roger and Garnier, and many others, the most important recent contribution being that of F. de Quervain.[1]

When the thyroid was supposed to have no functional importance, or only

[1] *Die akute, nichteitrige Thyreoiditis*, etc., Jena, 1904.

a mechanical function, the gland was neglected by pathologists. Even after the importance of the thyroid function became known the organ was rarely included in the routine postmortem examination. Within the last ten years, however, more attention has been paid to the thyroid at autopsies, and the influence of various infectious diseases and intoxications upon the thyroid has been cleared up to such an extent that a beginning can be made in establishing the relation of intoxication and infection to the thyroid gland, and in the elucidation of the clinical features of such cases.

Classification.—No satisfactory classification of the toxic or infectious diseases of the thyroid can be made at present. An etiological classification is still inaccessible, because even when the thyroid affection follows a disease of known etiology, such as influenza, it may be due to a different infection, the exact nature of which cannot always be determined. A division into "toxic" and "infectious" processes is equally beyond our present knowledge. The distinction between "simple" and "purulent cases" is important clinically, but neither sufficient nor accurate pathologically.

For the present it will suffice to speak of the various causal factors, using the term thyroiditis as a convenient one for both toxic and infectious cases.

Etiology.—*Age and Sex.*—Most cases reported as thyroiditis occur between the twentieth and fortieth years. The processes following infection will of course fall in the period at which those diseases chiefly occur, often in early life. The statistics at present show a slightly greater number of cases in females. Epidemics of simple thyroiditis have been reported by Brisson and Demme. The cases of the latter followed measles. De Quervain questions the correctness of the diagnosis in the cases of Brisson.

As *predisposing* causes, everything that may lead to congestion must be admitted. Among these we find trauma, including strangling attempts and the carrying of heavy loads upon the head. The "cold" and "rheumatism" of earlier times will be recognized now as infections of obscure but undoubted microbic nature.

Among *exciting* causes we know at present a number of kinds both organized and chemical. The latter may be of bacterial origin, or may be poisons from without, such as alcohol, or poisons formed in the metabolism of the body. The microbic cases are called primary when the disease begins in the thyroid, secondary when the thyroid becomes involved after disease makes itself manifest elsewhere. Even in the so-called primary cases the exciting cause must have come from some other place, although the source or place of entrance is not known.

Among infectious diseases accompanied or followed by thyroiditis are typhoid fever, smallpox, scarlet fever, measles, diphtheria, cholera, influenza, acute rheumatic fever, various infections of the nose, pharynx, and tonsils, erysipelas, puerperal fever, and malaria. In many cases cultures are negative; in some, with known causes, bacteria have been found in the thyroid different from those of the primary disease. Caccia has reported a streptococcus abscess in the thyroid of a twenty-two months' child, which began eighteen days after vaccination. The latter had severe local and general reactions. From observations of Combe and Rie, it seems that infections during pregnancy may affect the thyroid of the fetus.

Besides the cases recognizable clinically as thyroiditis, many cases have been recorded in which the anatomical changes of thyroiditis were present, although in milder forms. These can be spoken of as toxic thyroiditis or

toxic degeneration of the thyroid. In acute infections, such as scarlet fever and smallpox, less so in measles, there are marked alterations of a hyperplastic character, with hyperæmia, increase of colloid in the lymphatics, and arteritis or phlebitis with thrombus formation. In diphtheria the change is not constant. Small size of the vesicles, desquamation, and absence of colloid have been observed. Similar changes have been found in pneumonia, sepsis, osteomyelitis, erysipelas, purulent peritonitis, etc. In tuberculosis Roger and Garnier, Torri, and de Quervain have found sclerotic processes in the stroma. Torri found the connective tissue myxomatous. Alcohol probably causes similar changes. In many bodies with a history of alcoholism there was also other disease that could have affected the thyroid. Cachectic diseases, like cancer, diabetes, nephritis, Addison's disease, do not seem to affect the thyroid as distinctly as do the others mentioned. Besides alcohol, as an example of a poison from without, phosphorus can be considered a thyroid poison on the ground of animal experiments. Iodine may be capable of exerting a toxic action on the thyroid, but our knowledge in that respect is very scanty.

The question is important, whether the effects on the thyroid by toxic substances, either of bacterial origin or otherwise, are due to the irritating action of the poisons on the gland, or to compensatory processes set up in the organ in order to combat the toxic material. This question depends for its solution upon the real nature of the thyroid function. Tavel and Garnier endeavored to answer it by experiments, but with contradictory results.

Pathology.—Thyroiditis can be classified anatomically as simple or purulent, and each of these can be subdivided into parenchymatous, interstitial, or diffuse.

Simple Thyroiditis.—As in other organs, inflammation of more than the mildest degree sooner or later affects the connective tissue and vessels, but in most simple inflammations the parenchymatous changes are more marked, and much alike even when the causes are different. The epithelial cells project into the lumen of the vesicles or desquamate, filling the lumen more or less completely. At the same time there is increased growth of cells from the walls. The colloid becomes more liquid, and shows in hardened specimens granular material, vacuoles in large numbers, and often a stringy or meshwork appearance. Complete disappearance of the colloid is often noted. While granular or fibrillar changes are due to fixation, they are more marked than similar hardening solutions ever produce in normal colloid. The colloid also stains better with acid dyes, such as eosin or picric acid, than with hematoxylin or acid fuchsin. The desquamation of epithelial cells is only the exaggeration of a normal process, and is more active in other pathological conditions, such as congestion, as well as in intoxications and infections.

In the vesicles, and also in the interstitial tissue, round or polynuclear cells occur, and de Quervain also found foreign body giant cells. The changes in the connective tissue show various stages of infiltration, going on to new formation. The bloodvessels share in the inflammatory process. The lymphatics are also concerned, and, besides the ordinary changes of inflammation, show colloid or colloid-like material in various amounts.

It is not always easy to make a histological diagnosis between acute thyroiditis and some goitres. In case the greater part of the gland is involved, a careful comparison will usually show points of difference as

compared with various forms of goitre, but if the process is focal it may be impossible to decide the question.

Purulent Thyroiditis.—Purulent thyroiditis is rare, but sometimes follows pyogenic infections. Weil saw a case with a pure culture of typhoid bacilli four years after typhoid fever. It may begin in the vesicles or in the connective tissue. The abscesses may be single or multiple, may be small, without severe phenomena during life, or may be large and cause such processes as are described below among the complications of goitre.

Symptoms.—In cases of infectious thyroiditis there is no constant relation between the primary disease and the form or severity of the thyroiditis. This is especially true of the cases occurring after pharyngitis or rheumatic fever, which have often been mild, but sometimes severe, as in a case reported by Illoway.

The clinical features usually begin suddenly, with chills or chilly feelings and the other subjective symptoms of an acute fever. By the end of the first day or at the latest the second day there is a sensation of fulness in the throat, and at times difficulty in swallowing. With the feeling of fulness there is often a characteristic pain, radiating to the ears, occipital region, and teeth, or even to the shoulders and chest. Such a pain is present at times in cases of malignant goitre, and in persons who undergo thyroidectomy without general anæsthesia. By the second day there is a swelling corresponding to the part involved. In acute infectious diseases without marked evidence of thyroiditis (scarlet fever) Garnier found an increase of 1 to 2 cm. in the circumference of the neck. The swelling is usually one-sided, the right lobe being affected more commonly, then both sides, less frequently the left lobe alone, the isthmus very rarely. The swelling may begin in one lobe and gradually spread so that both sides are involved at once, or it may subside in one and then appear in the other. The size of the swelling varies greatly, but may measure several centimeters in diameter. The gland is hard, as a rule, sometimes elastic, rarely doughy in simple cases. It moves with the thyroid cartilage and trachea in breathing and swallowing. The skin over the tumor is sometimes not altered in color, but in severe cases it is red, with swollen veins, and sometimes œdematous. In a case of erysipelas the redness began over the thyroid swelling and spread from there. The affected gland is tender on pressure. Subjective sensations are slight in mild cases, but in others there is, in addition to the symptoms mentioned, dyspnœa, fulness of the head, headache, dizziness, even delirium. Hoarseness is sometimes present, due to an implication of the recurrent laryngeal nerve or an associated laryngotracheitis. Epistaxis sometimes occurs. According to the seat and extent of the swelling, there may be congestion or cyanosis of the face, enlargement of cervical veins, displacement of neighboring organs, and interference with the movement of the head and neck from pain in or pressure on the muscles. Irritation of the sympathetic nerve may produce ptosis, miosis, or cessation of perspiration. Difficulty of swallowing may be so severe as to require artificial feeding. The temperature and pulse are usually only moderately affected, unless by the associated or primary disease.

Course and Outcome.—Simple thyroiditis usually subsides in a few days or a week at most. Relapses sometimes occur, or delayed resolution, so that the course may be several weeks or months, and the gland finally resume its original size. Resolution may occur even when the swelling and local

and general symptoms have been most severe. Suppuration occurs in a large proportion of severe cases. In such cases the temperature is higher, chills may be repeated, redness and swelling become more pronounced, œdema or fluctuation develop in a circumscribed or diffuse form. In such cases rupture may take place externally or into the trachea, œsophagus, or mediastinum. "Dissecting thyroiditis" sometimes occurs. Gangrene is a rare result of thyroiditis; after extensive destruction healing may occur without loss of function. Death sometimes occurs from thyroiditis, either from asphyxia from compression or from rupture, or from exhaustion due to severe infection.

Remote Effects.—An important question for the future to solve is the relation of thyroiditis to myxœdema and Graves' disease. Remlinger has reported a case of acute myxœdema which may have had such an origin. It is well known that Graves' disease often begins with symptoms that suggest an acute thyroiditis or strumitis, and when we consider the mild symptoms of many cases of thyroiditis in acute infections it seems likely that not a few cases of so-called primary Graves' disease may have had their origin in that way.

Diagnosis.—This depends upon the recognition of the symptoms and the physical signs of the disease. Congestion, hemorrhage, goitre, malignant disease, also syphilis and tuberculosis, must be considered in the differential diagnosis. Other tumors of the neck, perhaps aneurisms, may have to be excluded. Congestion and hemorrhage can usually be distinguished by the absence of fever and general symptoms, and the local peculiarities. Goitre, especially acute goitre, may be impossible to distinguish at first, but the history, the possibility of detecting an infection or intoxication, the endemic occurrence of goitre, will soon serve to make a correct diagnosis. Riedel and Tailhefer have reported cases of chronic induration in which the differentiation from malignant disease was impossible. In such cases excision should not be delayed, but the diagnosis should be based upon the results of the examination of the excised gland. In all cases the course of the disease is important to follow. In all severe cases early and thorough use of the exploring needle, with aspiration, under complete aseptic precautions, should be practised. In one case of Breuer's, although the process seemed simple, there was a staphylococcus abscess in the gland.

Prognosis.—This must consider the near and remote outcome. The former is usually in proportion to the severity of the clinical phenomena. The latter cannot be determined in any case, but patients who recover should be advised about the need of careful examinations whenever symptoms of any kind occur in future.

Treatment.—In simple cases rest, mild diet, attention to the bowels and to other symptoms that may be present, and, locally, an ice-bag, usually suffice. Counterirritants, poultices, and massage should be avoided. Antipyretics are not indicated, but salicylates can be used in pyogenic or rheumatic cases; quinine in malarial cases (with parasites in the blood). Morphine or hypnotics may be advisable. Suppurative cases should be treated surgically, by incision, with or without drainage, according to the condition. Aspiration should not be used for treatment in such cases.

Tuberculosis.—The occurrence of tuberculosis of the thyroid gland was formerly considered rare, but since the investigations of Chiari (1878) it has been shown by many writers that in tuberculous individuals the thyroid

is involved to a notable degree (Chiari, 6 per cent.; Fraenkel, 10 per cent.; Hegar, 3.6 per cent. in 1563 cases).

The commonest form is miliary tuberculosis. This occurs in all cases of general miliary tuberculosis, and also in other cases. It affects a part or all of the gland. The latter is rarely enlarged. Degenerative or productive changes take place to a slight degree around the tubercles. In the chronic fibroid induration of the thyroid, described by Roger and Garnier,[1] in tuberculous subjects, tubercles and tubercle bacilli are not to be found as a rule. The authors ascribe the sclerosis to a primary degeneration due to toxins carried by the blood.

Nodular tuberculosis is rarer than the miliary form, but much more important clinically. It may with much reason be called struma tuberculosa.[2] In several cases, some of which are more than doubtful, the thyroid seemed to be the primary seat of tuberculosis. The thyroid is enlarged, usually causing a tumor externally. This, from its hard, nodular character and its rapid growth, has often been mistaken for a malignant process. In other cases the mass grows internally, sometimes causing compression and stenosis of the trachea. On section, nodular tuberculosis of the thyroid shows tuberculous tissue in various stages. Compression and interstitial inflammation of the neighboring gland occur in varying degrees. Calcification sometimes occurs in the sclerotic connective tissue. The caseation may be in small foci, or sometimes in large quantities (60 grams in a case of Schwartz). Bacilli are usually scanty, or may escape the most thorough search, even when the histological picture is typical. In some cases the tuberculosis grows in an old goitre.

On account of the impossibility of distinguishing the nodular form of tuberculosis, the grave suspicion of malignancy, and the possibility that if tuberculous the growth is primary or that it may break down and form large cavities, extirpation is always indicated. In case the growth causes tracheal stenosis, or pressure on nerves, extirpation, of course, should be done. In some cases there are symptoms of Graves' disease, as will be mentioned in the section on that disease.

Actinomycosis.—Actinomycosis of the thyroid has been observed. Koehler[3] saw a case in which a woman, aged twenty-five years, a dairy hand, had characteristic ulcerating actinomycosis for nine months, part of the time under treatment, before he did a radical operation followed by transplantation. Symptoms of myxœdema began three months after the onset, and became pronounced, but subsided after the operation.

The proper *treatment* of such cases is surgical. Potassium iodide may be used in addition, internally as well as in local or parenchymatous injections.

Syphilis.—The recognition of syphilis of the thyroid is comparatively recent, the most authoritative work being that of Engel-Reimers,[4] who observed swelling of the thyroid in half the cases of recent infection. Women were more frequently affected, in the proportion of 56 to 45. The swelling begins early, in the secondary incubation stage or during the period of secondary rash. It is soft and painless. Specific treatment has very little effect,

[1] *Archives gén. de Méd.*, 1900, vol. clxxxv, n. s. iii, p. 385.
[2] Bruns, *Beit. zur klin. Chir.*, 1893, x.
[3] *Berl. klin. Woch.*, 1894, p. 927.
[4] *Jahrb. der Hamburgischen Staatskrankenanstalten*, 1891–92, iii, 430.

the swelling going down very slowly. Mauriac, however, saw the enlargement of early syphilis subside quickly in one case.

Gummata sometimes occur, especially in newborn, congenital syphilitics, in whom Birch-Hirschfeld found characteristic lesions from the size of millet seeds to that of peas. In tertiary syphilis the process may involve the whole thyroid gland, and may be associated with symptoms of Graves' disease (Demme) or myxœdema (Koehler). As in tuberculosis of the thyroid, syphilis sometimes has a rapid growth, and may simulate malignant disease. Pain or dyspnœa, from pressure on the trachea or the recurrent laryngeal nerves, may occur. Perforation into the trachea has happened. In a case reported by Clarke, an ulcerating gumma of the isthmus caused œdema of the glottis, requiring laryngotracheotomy. Recovery followed.

Diagnosis.—The diagnosis of syphilis of the thyroid presents no difficulty when there is a clear history or other evidences of the disease. Late isolated lesions or congenital cases are much more difficult to recognize, and the former can usually not be diagnosed without histological examination.

Treatment.—Specific treatment is of course to be used if a diagnosis or even probable diagnosis can be made, but time should not be lost before advising surgical treatment, in case there is not positive improvement.

Echinococcus.—Echinococcus of the thyroid is rare, even in countries where the disease is frequent in general.[1] Infection usually takes place through the blood, but in one case (Meinert) it was supposed to be due to the licking of a wound in the patient's neck by his dog. Simple and multilocular cysts occur, with the secondary and degenerative changes common to echinococcus elsewhere.

Symptoms.—The course is chronic. The symptoms are slight at first, and the process resembles cystic goitre in its chief clinical features, and is usually so diagnosed. Hydatid thrill is rarely observed. Urticaria is frequently present when the cyst decreases in size. Compression of the trachea may occur, as with other kinds of enlargement of the thyroid. Suppuration and necrosis are not unusual. O. Ehrhardt reported a case of retrosternal echinococcus cyst in which it was impossible to tell whether the infection began in the thyroid and grew down, or in the mediastinum, becoming adherent to the thyroid.

Diagnosis.—The diagnosis is rarely possible without puncture and examination of the contents of the cyst.

Prognosis.—The prognosis is unfavorable. Perforation may occur at any time. According to von Eiselsberg, 4 out of 18 patients died, although the cysts were not larger than an orange.

Treatment.—The treatment is operative, by extirpation or partial thyroidectomy. Puncture with or without medication should never be used for therapeutic purposes in such cases.

Tumors.—Histologically, as well as clinically, it is always difficult, sometimes impossible, to distinguish the various forms of benign goitre from malignant newgrowths. This difficulty explains the fact that our knowledge of the subject is very recent. The real history of sarcoma of the thyroid began with the work of Kaufmann, in 1879. Morf collected 40 cases in 1899; Lartigau, 15 more in 1901; Ehrhardt,[2] in 1902, raised the number to

[1] Vitrac, *Revue de chirurgie*, 1897.
[2] *Beiträge zur klin. Chir.*, Band xxxv.

about 100, and at the same time collected the histories of about 150 cases of carcinoma. Benign connective tissue neoplasms, fibroma and lipoma, are so rare as to be without clinical interest. The "fibromas" described by Delore and Ricard were probably sarcomas.

All kinds of malignant thyroid tumors occur more frequently in goitrous regions and in persons with previous goitres. In Bern, Limacher found sarcoma 44 times and cancer 38 times in 7461 autopsies. Chiari, in 7700 autopsies in Prague, found only 5 sarcomas and 11 cancers.

Both primary and secondary tumors occur, but the primary forms chiefly concern us now. Sarcoma of the thyroid occurs sometimes in early life, as it does in other regions, but there is an unusual tendency for it to occur late in the subjects of goitre, the sixth decade being most frequently concerned. This unusual condition has been explained (Morf) by the atrophy of the parenchyma allowing the connective tissue to grow with unusual energy. Cancer of the thyroid is most frequent between forty and sixty, but sometimes occurs in early life. Men are less frequently affected than women, as is the case with simple goitre. The real causes of thyroid neoplasms are unknown. Traumatism and the toxins of infectious microbes (streptococci) have been alleged, but their relation must be slight.

All kinds of *sarcoma* have been observed, especially the round-celled and spindle-celled varieties. Lymphosarcoma seems relatively rare. Melanosarcoma is also rare. In one case E. Fraenkel found it with general sarcomatosis and thought it primary, but this seems doubtful. The spindle-celled forms are sometimes associated with bone formation (osteosarcoma), or the metastases of spindle-celled sarcoma may appear as epulis (Foerster, Pick). Angiosarcoma (perithelioma) or endothelioma may produce alveolar or cavernous growths. Diffuse sarcomatous degeneration of the thyroid has been described by several writers (Tornatelli, Weil, Bowlby, Sieveking). In general, such processes can be attributed to fusion of single nodules.

The combination of sarcoma and carcinoma of the thyroid is rare, but sarcoma of a goitrous gland sometimes produces the picture of sarco-adenoma or sarcocarcinoma. Saltykow[1] has reported such a case in which he believed the sarcoma was the original tumor, carcinomatous change then occurring, to produce not a mixed tumor, but two tumors, in an already goitrous gland. A similar view has been advanced by Woelfler.

Carcinoma of the thyroid occurs in several forms, sometimes easy to distinguish, but often not. The most frequent is the medullary (alveolar, cylinder celled) carcinoma, in which alveoli of various sizes and shapes occur, with proliferation of epithelium. The alveoli contain colloid material. The stroma has the usual characteristics. Sometimes cysts occur, and these are occasionally papilliferous. Congenital cystadenoma has been observed.

Adenocarcinoma of the thyroid sometimes produces histological appearances like those of medullary cancer, but more frequently it is adenomatous, having the type of adult or fetal thyroid tissue. In the latter case there are solid strands of epithelial cells in which neither follicular structure nor colloid are present. The connective tissue contains few nuclei; the bloodvessels are usually abundant. Sometimes the newgrowth is circumscribed, sometimes it resembles a local or diffuse hypertrophy of normal gland tissue. The

[1] *Centralbl. f. allg. Pathologie und path. Anat.*, 1905, p. 547.

pathological features of these growths are of great interest, and have engaged the attention of many investigators, notably Cohnheim, Woelfler, Neumann, M. B. Schmidt, and others. The clinical features are also of great interest, and will be mentioned later.

Scirrhus of the thyroid is very rare. It has occurred in young patients (twenty-six years in a case of Billroth's). Like adenocarcinoma, it may exist without enlargement of the gland, the central part being made up of dense scar tissue, the peripheral growth scanty. Squamous-celled carcinoma of the thyroid is so rare as to have no clinical interest.

Malignant tumors of the thyroid usually produce enlargement, which may be slight or may equal the size of an adult head. The right lobe is affected oftener than the left. The enlargement is smooth or lobulated, usually firm or hard, sometimes soft. It may be cystic and fluctuating, or vascular, and in the latter case, pulsating. It is usually translucent and glossy on section, sometimes granular, sometimes, in cancer, distinctly alveolar. The color is yellow or yellowish red.

Besides the regionary involvement, *metastasis* of thyroid tumors is very important. It may occur before local invasion, and in some cases causes all the discoverable clinical features. It takes place by the veins or lymphatics, or both, but in cancer, venous metastasis is relatively common, owing doubtless to the vascularity of the gland. The relatively slight participation of the lymphatics has been explained by the resistance of the capsule. However, carcinoma of the thyroid produces lymph gland involvement in about one-third of the cases, sarcoma in about one-sixth. The organs most affected by metastasis are the lungs and bones, less frequently the liver, kidneys, and pleura. Of the bones, the skull, inferior maxilla, and sternum are most often affected; the long bones of the extremities, and the pelvis next. No satisfactory explanation for the peculiarities of thyroid metastasis has been given. The metastases of thyroid cancer are also remarkable for their histological peculiarities. Thus, a carcinoma may have metastases containing normal looking thyroid tissue (also containing iodine).

Symptoms.—Both sarcoma and cancer of the thyroid may remain within the capsule for relatively long periods, causing symptoms like those of goitre, or, if rapid, those of thyroiditis or strumitis. The skin may long remain free from adhesion.

After invasion through the capsule or metastasis has occurred, the symptoms depend upon the direction taken and the seat of the metastasis more than upon the variety of tumor. Difficulty in swallowing from pressure upon or growth into the œsophagus sometimes occurs before dyspnœa, which may be due to pressure upon the trachea or involvement of nerves. Sometimes the tumor fails to follow the trachea in swallowing. Erosion into the œsophagus, larynx, or trachea may occur. Congestion of the veins in the neck is frequent, and malignant thrombosis sometimes occurs in such vessels. Bruns suggested removal of these for diagnosis. The proposal is all the more useful because, as Hahn has shown, thrombosis is rare in these vessels in simple goitre. Hahn and also A. Erlanger were able to demonstrate its value in cases of sarcoma. Œdema of the face and neck sometimes occurs. Hoarseness occurs from the implication of the laryngeal or tracheal mucosa, or from implication of nerves. Sometimes malignant vegetations form inside the trachea, and may lead to a diagnosis (tracheoscopy). Perforation and ulceration of the skin are rare. Pressure on

the nerves usually occurs relatively late, and may cause increase of dyspnœa and cough without expectoration. If the sympathetic is affected, there may be slight exophthalmos, miosis, loss of pupil reaction, and tachycardia. Paralysis of the arm has occurred. Pain in the occiput, ear, and shoulder sometimes comes on early. The course of sarcoma of the thyroid is usually short—from a few weeks to a year and a half, one year being the average duration. In medullary cancer the course is even shorter. In adenocarcinoma it may be very slow.

Among the *complications* may be mentioned especially perforation, necrosis, or hemorrhage from the larynx or trachea. Woelffler saw a case of sarcoma in which malignant thrombi extended down the large veins as far as the auricle. In a case of cancer reported by Hellandall, the growth eroded the sternum, caused thrombosis of the intrathoracic veins, and finally death by rupture of varicose veins in the œsophagus. Solis-Cohen reported a case in which implication of the right sympathetic nerve caused unilateral spasm of the laryngeal muscles. Later, the nerves of the opposite side became affected. Death followed from pneumonia. Tillaux has reported a case in which sarcoma of the thyroid was associated with symptoms of Graves' disease. The growth was removed and recovery followed, but death occurred later from metastases in the lungs. If the whole gland is involved in the newgrowth, myxœdema may develop, but its symptoms are less often noted than might be expected. This may be due to the fact that in the cancerous goitre secretion sometimes continues. Remittent fever is not uncommon in the later stages of carcinoma of the thyroid. Cachexia is often absent.

Adenocarcinoma, also called malignant adenoma of the thyroid, or adenoma destruens, differs in many respects from other thyroid tumors. The gland may not be enlarged, or it may be the seat of a long-standing goitre, without recent increase of size, and without local symptoms. Metastasis may be the first evidence of the process, and especially metastasis in bone, sometimes producing solitary tumors of large size, sometimes multiple tumors. The bones chiefly involved are the parietal, lower jaw, sternum, pelvis, and humerus. The tumor in the bone may grow very slowly, lasting six or eight years. Spontaneous fracture is likely to occur. Bony union sometimes occurs, but the writer saw a case in which there was no tendency to that or to the formation of osteophytes. Oderfeld and Steinhaus report a case that illustrates the course of the disease, and makes doubtful the belief in metastasis of normal thyroid or transplantation from normal thyroid which has been widely held. In their case tumors occurred in the cranium, with the structure of normal thyroid. As the gland itself felt normal, the tumors were considered the results of a sort of transplantation. A year later death occurred from other metastases, and a small encapsulated nodule was then found in the thyroid, evidently the primary tumor, although it had normal thyroid structure. The metastases do not always resemble normal thyroid or adenoma, but may be distinctly carcinomatous, or some of them may be adenomatous, others medullary carcinoma. In this respect thyroid adenoma resembles adenoma of the liver.

Metastases of thyroid cancers may not only repeat the structure of normal thyroid, but they may even be capable of carrying on the same function. It is even possible for cylinder-celled cancer of the thyroid to produce colloid and compensate for the loss of the thyroid after extirpation. Von Eiselsberg

reported an instructive case of this kind: A goitre was removed in 1886; symptoms of cachexia appeared, but improved distinctly with the appearance of a tumor in the sternum two years later. Four years afterward pressure symptoms made it necessary to remove the sternum and tumor, which was soon followed by tetany and later by cachexia. (The tetany has been explained in this case by accidental removal of an hypertrophied parathyroid gland.) The tetany slowly improved, but cachexia again appeared, and was not lessened by the growth of a tumor in the scapula. Death occurred in 1895 from marasmus. The sternal tumor was a cylinder-celled carcinoma with colloid. Von Eiselsberg rejects the idea that the carcinoma developed in a vicarious thyroid, although admitting the sternal tumor may not have been always of the same type.

Diagnosis.—The diagnosis of malignant disease of the thyroid is sometimes comparatively easy, as in case of rapid growth of a normal or, still more important, a goitrous thyroid, without symptoms of inflammation, but with involvement of skin or lymph glands or adhesion (not merely pressure on) to the œsophagus or trachea. Acute goitre sometimes closely simulates malignant disease. The writer reported a case in which a diagnosis of malignancy was made in a large indurated and rapidly growing goitre in a man aged sixty-six years. The subsequent course disproved malignancy. Such cases are always suspicious. Metastases add to the probability and usually contra-indicate radical treatment. The exploring trocar has been used to remove bits of tissue from the thyroid for examination. This is an uncertain method, and should not be used.

The probability of thyroid tumor should be considered in all cases of bone tumor, and if there is an old goitre, the probability is more likely to be correct than that of primary sarcoma.

Prognosis.—The prognosis is bad on the whole.

Treatment.—The treatment is purely surgical. If there is no evidence of metastasis, a radical operation should be made with transplantation or thyroid feeding. In some inoperable cases palliative treatment (tracheotomy) is indicated.

GOITRE.

Synonyms.—Struma; guttur tumidum *seu* turgidum (Latin); bronchocele; thyrophyma; thyrophraxia; Derbyshire neck; Nithsdale neck; Kropf; Blaehhals (German); Goître, grosse gorge, gros cou (French); gozzo (Italian); papera (Spanish).

Definition.—In general, any morbid enlargement of the thyroid gland, but more strictly, as in this section, a chronic enlargement of the thyroid gland of unknown cause, with variable anatomical features, occurring as an endemic, epidemic, or sporadic disease.

The synonyms illustrate some of the views regarding the nature of the disease. "Struma" (*struo*, to spread) and "goitre" (Latin, *guttur*, the throat) were applied indifferently for a long time to various swellings in the neck. In some countries these were chiefly tuberculous lymphatic glands, in others thyroid tumors. In England the former usage prevailed down to a very recent time. In Germany "struma" became the technical term for goitre. It was so used in the Alps at least as early as the sixteenth century. Medical writers, such as Fabricius Hildanus, took it up, and in 1789 Kortum gave

it a formal place in German medical literature. "Bronchocele," a very old term, indicates the belief that some goitres were due to hernial processes, or air in the tissue of the thyroid gland, an idea held as late as the end of the eighteenth century (Fodéré). Theoretically, we separate certain thyroid enlargements from the great group of goitres. In some cases, as malignant disease or inflammation, this is justified, but there are diagnostic difficulties that make such efforts imperfect in practice.

History.—The endemic occurrence of goitre has long been known. Pliny, Vitruvius, and other Roman writers mentioned it, and Juvenal used it in a rhetorical passage: "No one wonders at goitre among the Alps" (13th satire, 162). In the middle ages goitre was looked upon as a punishment for blasphemy, and the innocent, just as miraculously, were relieved of their thyroid strumas, as well as those of the lymphatic glands, by the royal touch. Marco Polo saw goitre in Central Asia. Paracelsus (1616) described it in the region of Salzburg, an important focus to this day, and made the first positive statements regarding cretinism and its relation to endemic goitre. In the next two centuries many eminent writers busied themselves with the study of the disease in various countries, but especially in the Alps and other mountainous regions. In 1789 appeared the important work of Malacarne, based on studies in the Valley of Aosta, and soon after it (1792 and 1800) the more influential treatises of Fodéré. In a work of this kind it is impossible to describe in full the historic development of so prolific a subject as goitre, and only a brief mention is given of the more important landmarks.

In 1810 Hausleutner settled the question as to whether the disease was in the connective tissue or the gland proper. Anatomical and embryological investigations were begun by Friedrich Meckel (1802), and continued by Huschke, Remak, His, Dohrn, W. Mueller, Koelliker, Woelfler, and many others. In 1820 Coindet announced the treatment with iodine, long used in other forms, and so began an extensive discussion on iodism and thyroidism that became still more pressing after the discovery of iodine in the thyroid gland by Baumann and the further chemical studies of Roos, Oswald, A. Kocher, and others. Schiff, in 1856, demonstrated that the thyroid gland was essential to life, and that it produced a substance necessary to the well being of the organism. This prepared the way for the observations and experiments of Langendorff, Huerthle, Horsley, and many later investigators. The early surgery of the thyroid was experimental, although it was not so realized until the discovery, by Kocher, of operative myxœdema, which served to stimulate further research. Finally, the names of Lebert, whose monograph (1862) was of great value, of Virchow (1863), who put the anatomical classification of goitre on a scientific basis, and of Hirsch, whose work on the historical and geographical relations of goitre will ever remain a classic, should be mentioned.

Geographical Distribution.—Goitre occurs as an endemic, epidemic, or sporadic disease. Sporadic cases may occur anywhere. Epidemics of goitre have often been observed, usually of small extent, of short duration, and in goitre regions. In strong contrast there are places where goitre is never absent and where it often exists in a large proportion of the inhabitants, in lower animals as well as in human beings.

The classic home of endemic goitre is in the Swiss Alps, and there it can most easily be studied at the present day. It is not uniformly distributed

even there. In Piedmont it sometimes affects more than two out of three of the inhabitants. In Canton Wallis, in the valleys of the Rhone and its tributaries, and in the city of Bern it is also very prevalent, although the figures furnished to Kocher, 80 to 90 per cent. among school children in Bern, are doubtless too high. In Tyrol, Styria, the Carpathian and other mountainous parts of Austria the disease is common. In the mountains of Germany there are many foci. In France, the Alpine departments, the Vosges, Cevennes, Pyrenees, and the high central plateau are affected. In Spain, the valleys of the Pyrenees, Asturia, and Galicia furnish foci. Sweden, Norway, Finland, and the Baltic provinces have a few endemic centres. In England, besides the traditional seat in Derbyshire, Sussex and Hampshire are affected. The mountains of Asia, Japan, and many of the Asiatic islands have numerous centres. Africa has foci in Abyssinia, and there are some in the Azores and Madagascar. The early explorers of North America found it among the Indians, as Munson has in more recent times, and in Esquimos. The region of the Great Lakes (Osler, Dock, Adami) shows considerable numbers. In Mexico and the mountains of South America it is not rare.

The absolute number of goitre subjects in countries with endemics of severe degree is of great social and economic importance. In France, Mayet (1900) estimates the number as 400,000. In all the Central European countries many recruits are lost to the military service on account of goitre. In Switzerland there were 12,277 in fifteen years, according to Ewald. In France 1200 recruits annually have been exempt, out of a total of 300,000 men. The drain on the country is better expressed by the number of cretins. In Cisleithan Austria there were, in 1883, a total of 12,815, or 71 per 100,000; in one district in Styria, a proportion of 1045 to 100,000. In Piedmont, Lombardy, and Venetia there were, in 1883, 12,882 cretins in a population of 9,565,038.

In the foci in the United States and Canada the goitres are, as a rule, not large, and cretinism is rare. Adami speaks of French Canadian villages in which scarcely a family is to be found that has not one or more goitrous members. The writer found 2 to 3 per thousand of well-marked cases in an extensive investigation, and 10 per cent. in young women, in a personal examination, most of them of small size. Munson found from 1.23 to 2.36 per cent. among Indians.

Etiology.—Whether sporadic, epidemic, or endemic, the cause of goitre is unknown. Of the numerous factors supposed to be effective, many, such as glacier water, have been abandoned. Others may assist in the production of goitre in regions strongly affected by the disease. Most of our knowledge is derived from studies in such localities, and it is more difficult to explain sporadic cases than those which occur in groups.

Age.—Goitre is rarely congenital, and when it is, it can usually but not always be discovered that the parents are goitrous or live in a goitre region. Congenital goitre is very rare in non-goitrous districts. In Switzerland Demme found 37 cases to 642 of acquired goitre. Hyperplastic, cystic, and mixed goitres occur congenitally. They sometimes cause difficulty in confinement. Acquired goitre occurs most frequently in childhood, before or about puberty. The tendency diminishes after the twentieth year, and cases rarely begin after forty, but a goitre acquired in earlier life may continue to grow, or may enlarge suddenly in later life, even at an advanced age. Acquired goitre occurs at all ages. The incidence (per 1000 of

population) at various periods is well shown by the analysis of Bircher, from statistics of Baillarger (13,090 cases):

Age.	Males.	Females.
0 to 10	1.8	2.2
11 to 20	7.9	11.5
21 to 30	12.6	15.4
31 to 40	11.6	24.6
41 to 50	14.0	30.4
51 to 60	12.2	29.0
61 to 70	12.3	27.4
71 to 80	6.2	19.9

Sex.—Women have goitre more frequently than men. The proportion varies up to six or eight to one, the numbers being more nearly equal in severe endemic foci. Some of the reasons given for the difference are unsatisfactory, such as the carrying of burdens upon the head, or occupations that keep the head bent forward, as in lace-making. It is more probable that some preponderance is due to the relation of the sexual organs and the thyroid and the congestion due to menstruation and pregnancy, possibly even sexual intercourse. The last, according to tradition, influences the circulation of the thyroid. In affected regions goitres frequently increase rapidly in size during pregnancy, and especially in confinement, going down rapidly in the days immediately following. Lactation has in general no effect, though Niemeyer attributed some goitres to prolonged lactation. Lange made some interesting observations on goitres in pregnancy in a goitre-free district. He thinks there is a relation between enlargement of the thyroid and the renal affection of pregnancy, so that one excludes the other. A point of interest is the fact that iodothyrin has a good effect on the renal affection. Lange's observations on cats make it doubtful whether the parathyroids are not more concerned than the thyroids. An increase in the size of goitres at the climacteric has been asserted, but is probably rare. Freund believed that various affections of the uterus, such as fibroma and parametritis, caused thyroid enlargement.

That congestion, whether due to irritation of the sexual sphere or to mechanical obstruction, is of some importance can hardly be doubted. There is a widespread tradition that carrying loads on the head, especially if combined with the wearing of a tight collar, favors the development of goitres.

Infectious diseases, such as scarlet fever, are sometimes followed by goitre, but it cannot be supposed that the causes of any of the well-known infectious diseases produce many cases of goitre, and the same may be said of ordinary traumatisms, sometimes mentioned.

It is not necessary to discuss in detail the possibility of telluric, climatic, orographic, or hydrographic causes for goitre. The disease, in its endemic form especially, occurs in every latitude, at every altitude where people live, in various climates, on high mountains, in deep valleys, on plains at various elevations. Although the seashore is almost wholly exempt, Duncan (1905) reports as many as 20 per 1000 cases in the municipality of Macabebe, near Manila Bay, only a few feet above the level of the sea. At the same time the relation of goitre to locality has been noted always and in every place where the disease is endemic. Not only are the localities circumscribed (though not always small), but besides the natives, who become affected to a high degree, others who enter and live in such regions frequently acquire

the disease, while they, as well as natives, on removing to non-goitrous localities, often recover. These conditions apply not only to human beings, but to domesticated and wild animals as well. Epidemics of goitre illustrate the local influence. They occur in goitre regions, especially in garrisons or schools, they affect large proportions of those living together, but do not spread among people living near but not in the same area.

The facts that have been mentioned make it certain the cause must exist in the soil, water, or air. As regards soil, we owe to Bircher an interesting study of the geological relations of goitre. He finds that endemic goitre occurs over marine deposits of the paleozoic, triassic, and tertiary formations, not over eruptive rocks or the sedimentary formations of the Jurassic or chalk seas, or over fresh water alluvium. Kocher partly confirmed Bircher's observations, but believed important exceptions occur. Johannessen has found the conditions in Norway (with a small number of cases) practically as Bircher describes them, and Berry has done the same in England. The geological relations of goitre deserve wide study, in which not only the superficial features, but the exact stratigraphic relations, should be made clear. Even when that is done, it remains to be learned whether the rock as such, or some chemical or organic peculiarity of the soil, is really concerned.

That the cause of goitre is ingested with drinking water is a very old belief. Vitruvius and Pliny mentioned goitre wells, and we find the latter mentioned again from the sixteenth century on. Mungo Park is said to have found the belief in Africa, and Gage found a similar one in the West Indies in the seventeenth century. Recruits who wish to escape military service acquire goitre by drinking the water of such wells; on the other hand, families in goitre neighborhoods who drink only rain water have been known to escape; also others who drank no water, but only wine. Goitre streams or wells may also lose their qualities. Some rivers produce goitre at certain points, but not at others. Sometimes a water, previously safe, acquires goitre-producing qualities. In several places in Italy and Switzerland whole goitre districts have been much improved by the introduction of water from a non-goitrous region. Bircher shows how, in the Commune of Rupperswyl, the introduction of water from a non-goitrous region in 1884 was followed by a gradual drop in the proportion of goitrous school children from 59 per cent. in 1885 to 11 per cent. in 1895.

The study of the possible causative agent in the water reveals many facts of interest, but does not as yet permit positive conclusions. Various mineral constituents have been found—iron, lime, magnesia—and, interesting in view of the relations of iodine to the thyroid, a smaller proportion of iodine than in the waters of non-goitrous regions. Répin has found a high degree of radio-activity in the goitre waters of the Swiss Alps, due to radio-thorium.[1]

Many authors have assigned goitre to the infectious diseases before the causes of the latter were actually recognized. Miasmata were assumed by many authors, but these have no more certain foundation, so far as examinations of the water are concerned, than the "malaria des montagnes" of Gambetta.

In the development of microbiology the water of goitrous regions has revealed, as does that of other places, various algæ and bacteria, but although many of these have been experimented with, none produced goitre, although

[1] *La Sem. méd.*, 1908, p. 526.

the drinking of the same water has sometimes been followed by goitre in dogs and horses. It has been thought that the boiling of water lessens or checks the tendency to goitre, and the writer has seen the sequence in a number of instances of goitre in young people.

While many facts suggest a living agent as the cause of goitre, the conditions are by no means as clear as might be imagined. Adami[1] has pointed out some of the difficulties. "If there be infection, it must be of remarkable character, for in the first place the condition only shows itself in the majority of cases from the age of eight onward, and in the second place, if the individual be removed from a goitrous region sufficiently soon after the development of the disease, and before chronic and cystic changes have ensued in the gland, the tendency is for the enlargement to disappear. In other words, the infection, if present, must depend on local conditions, and does not tend to be progressive or self-propagating. We have, that is to say, to recognize a novel form of latent infection, if I may so term it; or have to suppose that so long as the individual remains in a goitrous region infection continues, and that the goitre is an indication of an imperfect neutralization of the germs and their products; once the individual leaves the region, there being no longer infection, the destruction of the germs is complete and the thyroid eventually returns to a condition of equilibrium."

Pathology.—The alteration of the thyroid in goitre is either diffuse or partial. The simplest form anatomically is that seen in mild endemic cases. In these there is a hyperplasia or numerical hypertrophy of the glandular tissue, usually with an increase of the colloid and a proportionate hyperplasia of the connective tissue and bloodvessels.

Many of the follicles resemble those in the developing thyroid. These may be few or many, in circumscribed areas or diffuse. In the former case it is difficult or impossible to differentiate between adenoma and hyperplasia. According to Virchow the hyperplasia begins in the epithelium of the normal follicles; Woelfler and Billroth derived it from the interfollicular embryonic tissue, but Hitzig's investigations confirm the earlier view. According to von Burckhardt, the so-called external capsule of the goitre, when present, is due to inflammatory processes in the perithyroid connective tissue. The internal capsule, derived from the membrana propria, is characterized by the number of its bloodvessels.

If the hypertrophy produces the gross and microscopic picture of an enlarged but normal thyroid, it is spoken of as a "parenchymatous" goitre. Such a goitre rarely reaches considerable size. A notable enlargement is almost always associated with an increase of the colloid in the follicles. As this progresses, the epithelial cells become shorter or even flat, the walls of the follicles become thinned, and may even disappear. Sometimes thin partitions can be made out in what seem at first glance to be large colloid areas. Proliferation goes on in the follicular epithelium, and both the size of the gland and the histological picture become more abnormal. Some follicles are very large, others of normal size; there are younger ones, as shown by the size and the appearance of the cells, in variable numbers. Such goitres are spoken of as "colloid."

The term "vascular goitre" is often given to growths in which the bloodvessels are disproportionately large and abundant. Such a condition is

[1] *Montreal Medical Journal*, 1900, xxix, 1.

seen often in the goitres of Graves' disease, but in this the vascular enlargement is peculiar. In ordinary endemic goitres general vascular enlargement is not marked, but in some cases there are local conditions that warrant the terms "struma vasculosa," "struma aneurismatica," and "struma varicosa." In many cases of goitre, as also in malignant disease and even in the normal thyroid, there is a marked tendency to degeneration of the bloodvessels, with endarteritis, hyaline change, and calcification. These alterations have been investigated by Jores, Budde, and Farner. They are not necessarily part of a general arteriosclerotic process. Inflammatory changes, on the other hand, are rare.

In some earlier accounts of goitre amyloid degeneration was assigned a part. It, as well as hyaline change, occurs, but rarely plays an important part in the enlargement. Calcification and even ossification (Lücke) occur in the fibrous tissues of goitres. In all goitres various changes are likely to occur by which the size and condition of the gland become materially altered. These changes are chiefly degenerative, or the results of processes subsequent to degeneration of various kinds. The most important are colloid and hyaline degeneration, calcification, hemorrhage, necrosis, and cyst formation.

True cysts are rare, and occur from the progressive dilatation of follicles, or the coalescence of several follicles from atrophy of their walls. If recent, such cysts are lined by epithelium, but that is absent in old and degenerated cysts. Papillomatous growths are not uncommon in such cases. The cavities contain colloid in different degrees of concentration, often mixed with blood cells and cholesterin. False cysts occur from the rupture or necrosis of the glandular or interstitial tissue, with or without hemorrhage, followed by change in the surrounding tissue as well as in the contents of the cavity.

The hemorrhagic cysts have been well described by W. I. Bradley.[1] He shows that the contents of hemorrhagic cysts always indicate their origin. In recent cases, or when the walls are thin, there is evidence of recent hemorrhage. When the walls are thick, or calcareous, the fluid is usually straw-colored. The walls of the cysts are fibrous, partly of new formation. They sometimes contain atrophied remains of gland tissue, as if there had been compression of the surrounding thyroid tissue, but they are not lined with epithelium. The contents consist of a thin, watery, glairy, or viscid fluid of pale yellow to purple color, containing pigment granules, leukocytes, or larger cells filled with coarse, highly refracting granules and cholesterin. Bradley ascribes the hemorrhages, whether old or recent, single or recurring, to rupture by traumatism or strain. The degenerations of bloodvessels in the goitrous thyroid make the suggestion very probable.

Fibrous goitres, so-called, are the results of chronic degenerative and inflammatory processes, sometimes nodular, rarely diffuse. Calcification is not uncommon in these. Hemorrhage is rare. Necrosis sometimes occurs. Hyaline degeneration of the connective tissue can produce the adenoma myxomatosum of Woelfler.

In long-standing goitres many or all of the changes described are present in various proportions and various stages of growth or degeneration.

Symptoms.—**Onset.**—Goitres are spoken of as acute or chronic. The former develop within a few hours, days, or weeks. The "summer goitres

[1] *Journal of Experimental Medicine*, 1896, i, 401.

of visitors in goitre regions," epidemic goitres, and some rare vascular goitres are of this kind. They often subside as quickly as they form. Chronic goitres grow slowly, but sometimes with great and rapid variations. A sudden enlargement in a chronic goitre is suggestive of hemorrhage or malignant change.

Goitres may be important clinically either by reason of their size or by causing symptoms that have no constant relation to size, but depend on the anatomical relations of the growth. The enlargement may affect the whole gland or one (unilateral) or both (bilateral) lobes, or the isthmus (median). The right lobe is affected oftener than the left, possibly from the relation of the veins on that side. The pyramid, the lateral horns, as well as aberrant or accessory thyroid tissue may also be involved, alone or with other parts.

Size.—Sometimes the enlargement is very slight. In fact, from the range of size of the normal thyroid, it is evident that the gland may be pathologically enlarged and still be below the average size. In cases without signs of deep growth it is customary to consider as enlarged any thyroid that, in a neck of average figure, causes an appearance of swelling. Many cases of this kind are not true goitres, but depend upon temporary congestion. They are without symptoms or even cosmetic importance, or rather they add to the beauty of the neck. However, there are clinical reasons for classing such processes as goitres unless the history and course show them to be otherwise. The term "thyrocele" has no advantage as a designation for such enlargements. The goitres of ordinary classification are usually from twice to four or five times the size of the normal organ or part, but may attain enormous dimensions, hanging down over the clavicles or chest, even to the waist or thighs.

Small goitres are often unnoticed by patients. In some a tight collar may call attention to one, or it may be revealed by a sudden increase in size. The latter can often be traced to a definite cause, such as strain (confinement), trauma, an infectious disease, or an inflammatory or neoplastic alteration.

The skin over a goitre is sometimes of normal appearance, sometimes it is red, especially if the collar is too tight, or shows dilated veins under it. Cyanosis is rare. The shape of the swelling varies with the seat and the presence or absence of cysts or other localized processes. The mass moves with the larynx and trachea in swallowing. The consistency varies from a soft or soft nodular to a fibrous or bony hardness. Thrills and murmurs are very unusual even in acute goitres without symptoms of Graves' disease, in connection with which they will be described.

Aberrant Goitres.—Besides goitres occupying or springing from the usual position of the thyroid gland and growing forward, there are others of great clinical importance. Sometimes these develop in accessory thyroid tissue, and are then spoken of as accessory goitres. Often it is impossible to determine whether an aberrant goitre is a true isolated accessory one or whether it is united with the gland by thyroid tissue (false accessory goitre) or by connective tissue ("alliirter Kropf" of the Germans).

Aberrant goitres may occur in any position where thyroid tissue grows normally, or in other localities as the result of accidental conditions, such as the weight of the enlarged mass. Various classifications have been given, such as an embryonic one by Woelfler, a regional one by Madelung, and

various clinical ones. In many cases, such as the submaxillary goitres, the conditions are purely surgical and need not be considered in detail here. Certain varieties are important on account of the symptoms they produce. This is especially true of lingual, retrovisceral, substernal, or intrathoracic (goitre en dedans, goitre plongeant), and intralaryngeal or intratracheal goitres. Wandering goitre and thyroptosis (A. Kocher) are interesting varieties related clinically to intrathoracic goitre. Aberrant goitre is especially important when there is no goitre in the usual position. On the other hand, if it is possible to determine the absence of a lobe or of the isthmus of the thyroid in the usual position, the symptoms may be readily explained by assuming the existence of an aberrant goitre.

Intralaryngeal and intratracheal goitres are chiefly interesting to the laryngologist. They occur with or without external goitre, as round or cylindrical sessile tumors, rising from various parts, from the posterior wall of the larynx to the origin of the bronchi. The mucosa is usually intact and smooth over the tumor, but in one case an exudate raised the suspicion of ulcer. Meerwein saw one associated with tuberculosis. It is generally believed such growths are due to embryonic remains, but Paltauf thinks they grow through the wall, and in this he is supported by Bruns. The duration of the disease is from a few weeks to fifteen years. Women have been found to have such growths four times as often as men. The age varies from fifteen to forty years. The histological variety of the growth is most often the colloid goitre. The subjective symptoms are those of gradually increasing dyspnœa. Laryngoscopic examination alone can prove the existence of the tumor. Bruns used thyroid extract as a differential diagnostic measure.

Symptoms Due to Pressure.—*Respiratory.*—The pressure symptoms of goitre may be classified according to the organs involved. One of the first of these is the trachea. The trachea may be flattened by the enlargement of one lobe, most dangerous being the anteroposterior flattening from pressure of an enlarged isthmus, or by enlargement of both lobes (sabre-sheath trachea), or narrowed by circular compression. The last is rare. The most serious obstruction is caused by substernal goitre. Kinking from a sudden enlargement is a dangerous condition. With any of the varieties of pressure, changes occur in the trachea and larynx—congestion of the mucosa, later hypertrophy, which may be especially marked on the vocal cords; atrophy of the fibrous or cartilaginous tissues of the trachea (Woelfler), or even softening. Tracheal and bronchial catarrhs develop in time, also emphysema. The symptoms from these changes are dyspnœa, especially on exertion, and a more or less marked stridor or cough. These symptoms vary much in intensity in different cases.

Besides the chronic obstruction there is an acute one, not always associated with chronic obstruction, due to pressure on the recurrent nerves, often spoken of as "goitre asthma." It often occurs at night, without previous symptoms, with intense subjective and objective dyspnœa. This may subside, to be repeated again and again, or may produce so-called "goitre death." More or less pressure on the recurrent nerves occurs in about 10 per cent. of cases of goitre (Woelfler), but the condition is not always severe enough to alter the voice. If there is marked pressure on one recurrent nerve the condition is dangerous, more so if both are affected. In some cases laryngospasm occurs in certain positions of the body.

Nerves.—The vagus is rarely involved in simple goitre. The sympathetic is also only rarely affected, but it may occur, with alterations of the pupils, of sweat secretion, and color and temperature of the face. The hypoglossal nerve is rarely affected, but is sometimes injured in operations, producing paralysis of the tongue. From pressure on the spinal accessory nerve spasm of the trapezius and sternocleidomastoid may occur.

Œsophagus.—Difficulty in swallowing is not frequent in benign goitre, but can occur from circular, or left-sided lingual or retrovisceral (between trachea and œsophagus) growths. There may be pain in swallowing or partial or complete obstruction, so that only fluids pass. In cases of lingual goitre hoarseness and the sensation of a foreign body may be associated with difficulty in swallowing.

Bloodvessels.—Venous congestion in the neck may be due to respiratory obstruction. More directly it is due to pressure on the veins. The latter are partly pushed out of the way, but in both arteries and veins the walls of the vessels become thinned and large goitres may compress the internal jugular vein or even the jugular bulb itself. With venous congestion and cyanosis there may be a striking pallor of the skin. Œdema of the mouth or of the arms is a rare event.

Heart.—The occurrence of palpitation of the heart in goitrous subjects has long been known, and dilatation has been observed, with or without myocardial changes. The relation of the heart to goitre was discussed as early as 1828, by Adelmann, according to Minnich.[1] Important observations were made by Potain, E. Rose, and others, but we owe our modern interest in the subject to F. Kraus (1899).

Minnich gave the term "goitre heart of Rose" to the process associated with venous obstruction and distention of the right heart. In some cases it was also supposed that pressure on nerves could produce cardiac alterations; for example, pressure on the vagus may cause slight acceleration, without enlargement. The cardiac alteration due to obstruction of respiration has been called the "dyspnœic goitre heart." A. Kocher prefers to call both these forms "mechanical goitre hearts," in distinction to the true goitre heart or "struma cardiopathica." There is a great difference of opinion in regard to the nature of the latter cases. Kraus, under the name "goitre heart," describes conditions such as occur in Graves' disease, and even associated with tremor, exophthalmos (slight), and other symptoms of Graves' disease, especially of the incomplete forms. He admits the similarity of the symptoms to artificial thyroidism, but denies their relation to Graves' disease.

Minnich, whose analysis of cases is very painstaking, follows von Cyon in considering Graves' disease one of hypothyrosis, and he also thinks goitre heart is a "thyroprive" condition. Kocher does not agree with this view. His belief in the relation of non-mechanical "goitre heart" to Graves' disease, based largely upon operative experience, is shared by the majority of English and American observers. Gittermann[2] has carefully examined cases observed in his Nauheim practice, and among 121 patients with goitre and heart symptoms, 11 were distinctly cases of Graves' disease; 8 of the

[1] *Das Kropfherz und die Beziehungen der Schilddrüsenerkrankungen zu dem Kreislaufapparat*, 1904.

[2] *Berl. klin. Woch.*, November 18, 1907.

others had mechanical causes, venous and respiratory chiefly. The other 102, true goitre hearts, he would assign to the group of Graves' disease. In long-standing cases he found signs of myocardial degeneration.

Although the real nature and classification of goitre hearts cannot be cleared up until our knowledge of Graves' disease is more perfect, it is important now in any case to search for evidence of Graves' disease on the one hand, of pressure on the other. Kocher has properly emphasized the importance of recognizing the mechanical cases early, in order to give relief by operative treatment before the heart has undergone degeneration. In non-mechanical cases it is important to realize the frequent failure of digitalis. Gittermann looks upon it as characteristic of the condition.

Hemicrania has been ascribed to goitre, but chiefly in persons predisposed to headache. Pain behind the ear may be caused by the pressure of a goitre on the posterior auricular nerve. Tinnitus aurium is sometimes a troublesome symptom.

In cases with large goitres the physiognomy of the patient is often changed by the alteration of the position of the head and the shape of the lower jaw and mouth. Changes of expression from Graves' disease and myxœdema or cretinism will be discussed in other places.

Complications.—Injuries of goitres are dangerous by reason of hemorrhage from the fragile bloodvessels, but especially on account of the possibility of bacterial infection. The latter is likely to occur also in puncture of the thyroid without aseptic precautions, or by indirect infection through the blood stream. It sometimes follows injections into goitres, even when asepsis has been observed. Various pathogenic bacteria are concerned in different cases, especially pyogenic cocci, pneumococci, typhoid bacilli, and colon bacilli. The latter have been found in a patient with constipation, apparently a primary strumitis. There is usually an intense inflammation of the connective tissue, infiltrating the follicles, and going on to abscess or necrosis of greater or less extent.

The symptoms are essentially those of inflammation, with severe radiating pain in the thyroid region, chills, fever, and rapid swelling of the thyroid, with great tenderness. The skin over the inflamed part becomes red, the veins congested, and the face cyanotic. Nosebleed is not rare. From the rapidity of the swelling, compression of the adjacent organs is inevitable, with pain, spasm of the glottis, dyspnœa, and cough.

The result of strumitis is usually suppuration or necrosis. Resolution is rare. Suppuration is accompanied by softening and fluctuation, with œdema of the skin. Perforation can occur through the skin, or into the trachea, œsophagus, or mediastinum. Erosion of the common carotid artery has occurred. After perforation recovery can occur. Troizki observed a case in which strumitis followed erysipelas in a patient with Graves' disease. After perforation externally, both goitre and Graves' disease disappeared.

Diagnosis.—The diagnosis of an enlargement of the thyroid, whether general or partial, is usually easy. The shape and position of the swelling, its relation to the great vessels and the sternomastoid muscles, its movement with the larynx and trachea in swallowing all serve to prove the thyroid origin of the mass. Other tumors, such as sarcoma of lymph glands and inflammatory swelling in or under the sternocleidomastoid muscle, can usually be differentiated by their physical peculiarities, especially by the absence of upward movement on swallowing, and by the history, the blood examination, and the course of the disease.

If the enlargement is in the thyroid, the exact condition should be ascertained as early as possible. This can be done only by a careful examination of the thyroid region, of other organs, and of the history of the case. The skin over the swelling must be examined with reference to alterations of color, presence or absence of adhesions, œdema, and enlarged veins. By palpation the consistency of all parts of the mass must be determined, and the existence of thrill and the presence of adhesions to other structures. In palpation it is important to examine with the patient upright as well as lying down, and to use both hands, so as thoroughly to outline the mass, to prevent it from slipping, and to get an accurate idea of the consistency. Auscultation is important on account of possible vascular murmurs, or stridor not otherwise detected. The larynx and trachea should be examined by the laryngoscope, to detect possible stenosis, congestion, paralysis of muscles or deformity. Skiagraphic examination is sometimes of value in showing deformity of the trachea.

The family history is often of interest, but is not essential to the diagnosis of simple goitre. In women the history of the sexual organs in relation to the goitre should be ascertained.

Simple hyperæmia of the thyroid is differentiated by the small size and symmetry of the swelling, the soft consistency, the history of one or more of the causes of that condition, and the course. It is important to remember that such a goitre is occasionally followed by some other form, especially Graves' disease. The search for thrills and murmurs, and for the other signs of Graves' disease, is imperative in all these cases.

Parenchymatous or follicular goitre is recognized by its greater hardness in some cases, but there are many mild conditions in which a differential diagnosis between this and the preceding form is impossible. The detection of nodular hard areas should raise the suspicion of parenchymatous goitre or fetal adenoma. Colloid goitres are usually large, often asymmetrical, of softer, somewhat doughy consistency. They occur in rather older patients than the varieties just described. Vascular goitre and the rare aneurismal goitre are generally easy to recognize. In the former, Graves' disease must be excluded. Fibrous goitre is distinguished by its hard nodules, strands, or masses. It is especially frequent in long-standing cases, and especially in the irregular or grotesque forms seen in severe endemic goitre, and is then only part of the process. Mixed goitres are recognized by their different consistency in various parts. Hard and rapidly growing areas, especially if nodular, are suggestive of malignant disease.

The existence of cysts in goitres is of great therapeutic interest. Large cysts with fluctuation are easy to recognize, especially if superficial. Small ones are impossible to detect by ordinary methods, and even cysts holding 10 or 15 cc., if in the midst of a large parenchymatous goitre, may be overlooked. In all doubtful cases a careful exploration should be made with an aspirating syringe, under aseptic precautions, using a sharp needle, and avoiding unnecessary traumatism. The existence of a cyst, or of multiple cysts, can be made out by careful exploration and examination of the fluid. A fluid resembling pure blood is important to examine microscopically. Cholesterin crystals, an excess of leukocytes, or large granular cells indicate cysts in such cases.

Aberrant goitres in the neck are often impossible to distinguish from other tumors or cysts. Extirpation is usually indicated, and the positive diagnosis

can then be made. Iodine treatment is sometimes useful, but should not be used for indefinite periods as a diagnostic agent.

Retrosternal and retroclavicular goitres should be suspected when there are attacks of suffocation, especially on lying down or while asleep, with physical signs of tumor in the upper part of the thorax, or when there are signs of thoracic tumor without a thyroid gland in the neck. Sometimes the relation of the growth to the thyroid above the clavicles can be shown by swallowing movements. The *x*-ray examination may be of service. Tumor of the root of the tongue should always excite suspicion of lingual goitre.

Prognosis.—Simple goitre is usually a chronic disease. Acute goitres, or small parenchymatous chronic goitres that have not lasted long enough to undergo degeneration, may recover under medicinal treatment or spontaneously, especially by leaving the locality in which the goitre was acquired, by changing the drinking water, or having it boiled.

In the case of long-standing goitres the course depends upon the position of the tumor, the presence or absence of pressure upon the trachea, œsophagus, nerves, and veins, and the occurrence of malignant change or inflammation. Position, and not size, is the important factor in such cases. Increase of pressure sometimes occurs from sudden hemorrhage into the tumor or from sudden increase of the rate of growth, and may radically change the prognosis. Sudden death can occur in such cases from tracheal stenosis or heart disease, less frequently from complications in the bronchi or lungs, from spasm or œdema of the glottis, or apoplexy. Tracheal stenosis from pressure on the tumor by the muscles of the neck is a possible cause of death.

Treatment.—**Prophylaxis.**—The most important task in connection with goitre is prevention. In countries with endemic foci this is an economic problem not less important than the prevention of the common infectious diseases. Besides sanitation in its broadest sense, the prevention of goitre requires the elimination of special factors, if they can be found, such as water supplies, that play a part. If possible, persons in predisposed families should leave goitre districts and live in healthier localities. Drinking water should be boiled. Tight collars and occupations that induce congestion of the head should be avoided. Many of the assisting causes can, of course, not be wholly avoided. Treatment of the goitre is therefore necessary, because, in addition to the general indication, or the removal of deformity, there may be serious mechanical consequences or still more serious results of altered function of the diseased gland. Even a small goitre, diffuse or nodular, should be looked upon as serious, because it may cause pressure on important organs, or may lead to extensive atrophy from pressure in the healthy part of the thyroid, with functional disturbances.

The medicinal treatment of goitre is included in the one word iodine. This has been used for centuries, in the form of burnt sponge, and as the element of various salts since 1820, but we are only now beginning to understand the most efficient methods and the rationale of the treatment.

It has long been known that small, or recent goitres, those in young people, the parenchymatous forms rather than the more atypical goitres, are more amenable to treatment. A. Kocher has pointed out some interesting relations between iodine and goitre. In healthy persons ingested iodine is excreted almost completely in the first twelve hours. In cases of diffuse hyperplastic or parenchymatous goitres there is increased excretion of iodine; at

the same time the goitres diminish in size. Nodular goitres without degeneration act in the same way. Degenerated nodular goitres and mixed goitres do not as quickly subside, if at all, but the iodine excretion goes on as in healthy people. Colloid goitres do not become smaller, but the excretion is increased. Under long-continued treatment the colloid undergoes changes, and late improvement may occur. The goitres that diminish under iodine contain little iodine, and conversely.

From all that we know at present, it would seem that T. Kocher is warranted in calling iodine a thyroid tonic. It stimulates the morbid gland to healthy action, provided the condition is one of altered function and retention of secretions. It cannot be said to remove the cause of the disease directly, so that its specific character is peculiar.

So potent a drug is, of course, not free from danger. Under the name "iodism" a condition has long been known in goitre regions, occurring in certain people treated for goitre with iodine preparations. This is altogether different from the irritation of the mucous membranes seen in certain susceptible people under treatment with iodine or iodides. It is recognized now, as was suspected by Lebert long ago, as an intoxication by thyroid products, a thyroidism or artificial Graves' disease. Nervous excitement, loss of sleep, tremor, circulatory disturbances, with warm skin, sweating, frequent pulse, palpitation, vasomotor disturbances, asthmatic attacks, sometimes vomiting and diarrhœa—occur in varying degrees of severity. Emaciation follows if the condition continues, and a severe and fatal marasmus, such as ended the life of the botanist de Candolle, as described by Lebert. The severe cases are not so common now as they were in the early days of iodine medication, and depend to a certain extent upon a predisposition. It sometimes comes on very quickly, without disappearance of the goitre. It is especially likely to occur if iodine is used in excess, and the latter depends upon the relation between ingestion and excretion. Since rapid subsidence of a goitre is rarely necessary, and since we have no simple method of determining the rate of excretion of iodine, it is best to give the drug in small doses, at intervals.

In certain goitres, as mentioned above, recovery is easily brought about. With small, recent, congestive or hyperplastic goitres in young people a few applications of a solution or ointment of iodine over the gland often have an apparently miraculous effect. In larger or older goitres external treatment is often ineffective, the solutions are irritating, and the ointment disagreeable.

Solutions taken internally should be used, and 2 decigrams (3 gr.) of iodine daily (4 cc. or 1 fluidram of liquor iodi compositus) will produce a notable effect in favorable cases. With such a dose, three-fourths the amount will be excreted by the urine in forty-eight hours (A. Kocher), so that it is safer if used every other day. Smaller doses may be given daily, such as ten minims of Lugol's solution, corresponding to 0.1 gm. (1.5 gr.) of iodine three times a day, but the patient must be carefully watched. If the goitre goes down quickly, in one to two weeks, as it does in favorable cases, the treatment can be stopped. If not, interrupted administration is preferable, giving 0.1 to 0.2 gm. every day or other day for a week or two; stopping two weeks, and repeating as necessary. Even in colloid goitres the treatment is sometimes effective after a long time, even up to two or three months. Sometimes a goitre will promptly subside, but only partially, and

it can then be discovered that the condition is complicated, usually by a cyst, sometimes by a solid growth. Cysts, fibroid masses, calcified areas, and old goitres generally are not influenced by iodine, and it should not be given for them.

Iodine preparations have been extensively used by *injection* into goitres. The method is very dangerous, and should never be used until simpler methods have been tried. T. Kocher uses injections in the treatment of those goitres in which iodine may not reach the gland through the circulation, especially large colloid or nodular goitres. The tincture of iodine should not be used. Iodoform, ether, and iodoform oil are safer, still better 2 per cent. solution of potassium iodide, injected slowly (1 to 5 cc.). A different indication has been met by the injection of irritating solutions, iodine and others, into cystic goitres. This is less certain and more dangerous than extirpation. There is no advantage in using organic or other complex preparations of iodine rather than Lugol's solution or a simple tincture.

Thyroid, which has been used extensively since it was first advocated by Reinhold, often gives good results, but until there is some way of standardizing the preparations, thyroid must be looked upon as less exact than iodine and not essentially different. Iodothyrin has been extensively used also, but it is not to be preferred to inorganic iodine.

Goitres amenable to iodine subside quickly under *x*-ray treatment. In general there is no advantage in such treatment, although further observation may reveal special indications that can be met in that way.

In cases of goitre with severe symptoms it is proper to carry out more intensive iodine treatment under careful supervision, but only if the goitre is one that seems favorable for such treatment. In many of these, and in all cases not amenable to medicinal treatment, surgical intervention is necessary. In the hands of Kocher, Bruns, Kroenlein, Halsted, C. H. Mayo, and others the surgical treatment of goitre of all kinds has become a safe operation. The details belong to surgical works.

EXOPHTHALMIC GOITRE.

Synonyms.—Basedow's disease; Graves' disease; goître exophthalmique, cachexie exophthalmique (French); Basedow'sche Krankheit, Glotzaugenkrankheit (German); morbo di Flajani, struma *seu* gozzo esoftalmico (Italian); bocio exoftalmico (Spanish).

Definition.—Exophthalmic goitre is characterized by an alteration of the thyroid gland, which is usually enlarged, and by tachycardia, palpitation of the heart, protrusion of the eyeballs, or tremor, or any combination of these, with some or many other symptoms on the part of various organs.

History.[1]—Unnecessary confusion has been thrown around the history of this disease. From its obscure pathology and wide symptomatology the clinical picture was developed slowly. References to suspected cases can be found in the eighteenth century, as in Morgagni, but are by no means

[1] For the early history and bibliography of exophthalmic goitre, consult: H. Sattler, in von Graefe u. Saemisch, *Handbuch der ges. Augenheilkunde*, 1 ed., vi; Leopold Hirschberg, *Ueber die Basedow'sche Krankheit, Historischkritische Studie, Wien. Klinik.*, 1894; G. Buschan, *Die Basedow'sche Krankheit*, Leipzig u. Wien, 1894; P. J. Moebius, *Die Basedow'sche Krankheit*, 2 ed., Wien, 1906.

clear. The inadequate article by Flajani (1802) had no influence on later observers, as appears from the citations of Stokes (*Diseases of the Heart*). The first contribution of permanent value was made by Caleb Hillier Parry[1] (called "Percy" by Virchow and by Beigel in both the English and American editions of Reynolds' *System*), in whose posthumous works notes of eight cases are given, the first one, observed in 1786, being typical. Between the time of Flajani and the appearance of Parry's work, cases were described more or less imperfectly, especially in England and France. Soon after (1828), Adelmann, in Germany, reported two cases, with an autopsy. The next important report was that of Graves (1835), and on account of the fame of the Irish clinician the disease became widely known, especially after the appearance of his text-book in 1843—still more through the work of Stokes (1854), in which the observations of Flajani, Parry, and Graves were drawn upon, and in which the vascular peculiarities were accurately described. In the meantime (1840), von Basedow had published a fuller description and more complete analysis of four cases. Graves did not go any farther than Parry in the interpretation of the cases, although in one point especially he showed his clinical insight in realizing that the goitre was not the same as in the endemic disease. Basedow, like Parry, noted the "rheumatism" in the previous history. He observed the important symptoms—profuse perspiration, nervousness, restlessness, the precipitate speech, headache, subjective warmth, and air-hunger. He noted improvement in pregnancy. In explaining the exophthalmos, he avoided the error of Stokes (probably held also by Graves), according to whom the condition was an increase of vitreous and aqueous humors, and believed in a "strumous hypertrophy" of the tissues behind the bulb. Trousseau, who had seen a case as early as 1833, later (1860) advocated giving Graves' name to the disease. Before that time many of the names applied were too absurd or too cumbrous to deserve perpetuation. Trousseau, however, was anticipated by A. Hirsch (1858), who advocated, and Fischer and Charcot (1859), who used, the name "Basedow's disease." About the same time the term "goitre exophthalmique" (Trousseau, Aran, Hiffelsheim) began to replace "cachexie exophthalmique" in French, and soon after in English, medical literature.

The question of *nomenclature* really has to deal with these two terms. "Basedow's disease" is becoming more and more general. "Graves'," on grounds of priority of description, is not as appropriate as "Parry's disease," and if we leave priority of use, the customary rule, and take the name of the first observer, we have an endless and unprofitable task. "Exophthalmic goitre" avoids the eponymic Charybdis, but strikes the Scylla of barbarism. This is its chief drawback. It avoids all controversy as to pathology, and if it be said to be inexact, in that both goitre and exophthalmos may be absent, one can point to similar exceptions, as in "typhoid fever" without fever or typhoid condition. If "Basedow" be preferred, it should be pronounced Bas-e-do.[2]

[1] *Collections from the Unpublished Medical Writings of the late Caleb Hillier Parry*, London, 1825, vol. ii, p. 111. "Diseases of the Heart" (chapter head). "Enlargement of the Thyroid Gland in Connection with Enlargement or Palpitation of the Heart."

[2] The writer has reviewed the early literature with citation of original articles in the *Journal of the American Medical Association*, October 3, 1908, p. 1121.

Modern History.—The later history of exophthalmic goitre can be epitomized by noting the work of Charcot and Trousseau (1860) on the "incomplete" ("frustes") forms of the disease, of the discovery of the importance of tremor by Charcot (1862) and Marie; the more accurate study of the eye symptoms by Desmarres, von Graefe (1864), and Stellwag; the studies of the nervous and electrical conditions by Chvostek senior. Later came the work of Moebius, the application by Rehn and himself of the antimyxœdema theory, and finally the more accurate pathological anatomical era and the stage of surgical treatment with its revelations. Many historical details will have to be alluded to in the following pages.

Etiology.—*Frequency.*—The belief in the general rarity of exophthalmic goitre is rapidly giving way. As Charcot said, we see what we know, and it is remarkable how even at this day well-marked cases are occasionally overlooked. Paessler, in Jena, saw 58 cases out of 2800 patients. The writer had 52 typical cases out of 5000 medical cases.

Sex.—Women are much more subject to exophthalmic goitre than men. Eight to one is probably the usual proportion in large series of cases, although Buschan, in 980 cases, found it 4.6 to 1. In Murray's 180 cases there were only 10 men.

Age.—Most cases occur between the ages of sixteen and forty. Cases in childhood are rare, but have been observed from the third year on. After fifty the incidence in general is rare, and men then are relatively more often affected (1 to 3, Buschan).

Marriage and occupation seem to be unimportant in the etiology.

The family history is unimportant in most cases. In goitrous regions goitres are often to be found among mothers and sisters of patients with Graves' disease; occasionally an immediate relative, as mother, sister, or brother has Graves' disease. Rarely, a stronger family disposition is encountered, as in the experience of Oesterreicher: eight out of ten children of an hysterical woman had Graves' disease, and one daughter had three children with the same affection. In another instance, grandmother, father, two paternal aunts, and brother and sister were affected. Moebius looks upon the occurrence of simple goitre, often unnoticed, among the relatives of patients, as suggesting a congenital alteration of the thyroid, that can be converted into exophthalmic goitre by the influence of infection (typhoid fever, syphilis).

The relations of locality and climate are obscure. The incidence of exophthalmic goitre seems to vary in different parts of the world, being higher in England and on sea coasts than in some continental localities, but it is very high in the interior of North America. It is sometimes said that endemic goitre districts are relatively free from exophthalmic goitre, but this is not true of Switzerland and France or of the region of the Great Lakes of North America.

Among the traditional causes of exophthalmic goitre *fright* has always occupied a prominent place. This view is doubtless assisted by the resemblance of a typical Graves' facies to the picture of fright. Actual fright, sudden or prolonged, must be a rare cause, but various emotional shocks seem to have close relations in many cases. Careful inquiry often discloses the probability of the disease being in existence in a mild or latent form before the shock. Thus, one woman, aged twenty-five years, had palpitation of the heart for some months, following influenza. She was then frightened by thinking her child had drunk carbolic acid, had so rapid a heart

beat that she was supposed to be dying, and was confined to bed for three months with tachycardia, nervousness, and weakness.

A long-continued history of *worry*, with or without adequate cause, is often given. Hard, physical labor, with worry, or with loss of sleep and insufficient food, can sometimes be traced. In some cases prolonged dancing has been given as a cause. Buschan especially has given many proofs of the neuropathic origin and relations of exophthalmic goitre, but probably this has been exaggerated as a causal factor. Many patients give a history of "nervousness," or "nervous prostration," long before the other symptoms. Many are neurotic looking. But many others are free from such phenomena until the onset of the exophthalmic goitre. There are comparatively few who have hysterical stigmata or histories, nor are they easily influenced by suggestion, if we except the frequent response to treatment of any kind for the Basedow symptoms. Even then they are not equally suggestible in regard to all symptoms—*e. g.*, their constipation is often refractory to psychic treatment. The writer has been especially impressed with the above view because his goitre patients of all kinds live in a region where neuroses are common, but the neurotic subjects and families are much more likely to have gastric or sexual neuroses than exophthalmic goitre. Many of them also have small, simple goitres, but do not show Basedow's signs to a notable degree after taking iodine or thyroid extract.

"Colds," sore throat, tonsillitis, or other acute infections often precede the symptoms of exophthalmic goitre. In some cases a swelling of the thyroid during or after the acute disease suggests acute thyroiditis. In patients with simple goitre an acute inflammation sometimes seems to form the connecting link with Graves' disease. Thus, a woman, aged thirty-three years, was treated for a parenchymatous goitre, which under small doses of iodine became so small as to be hardly visible. There were no signs of Graves' disease at any time during observation for three months, and medication was stopped. An operation for displaced uterus was undergone, with no untoward symptoms. Five months after treatment was stopped there was an acute sore throat. In about two weeks the thyroid became larger and painful. Without consulting any one the patient had a friend massage the gland. In a few days she had palpitation, thrill over the thyroid, weakness of the legs, and a belief in a change in her condition, followed in a few weeks more by many marked symptoms. The thyroid was only slightly enlarged, but was the seat of unusual thrill, murmur, and visible pulsations. There was Stellwag's sign, but no Graefe or Moebius sign. Engel-Reimers has called attention to the frequency of secondary syphilis in the early history of exophthalmic goitre in young married women. Other diseases that occur in a similar connection are rheumatic fever, typhoid fever, scarlet fever, measles, whooping cough, mumps, and malaria. One of the writer's patients had a striking history of exacerbations of Graves' disease with severe tonsillitis, a coincidence that has been observed by others.

W. B. Stanton[1] has called attention to the frequency of Basedow's symptoms in tuberculous subjects, and in the thyroid glands of fatal cases of tuberculosis he found tubercles in a notable proportion of cases. In the thesis of Dumas[2] a number of cases are cited. Hufnagel, in 1246 children,

[1] *American Medicine*, 1905, x, 605.
[2] *Goitre exophthalmique d'origine tuberculeuse*, Lyons, 1907.

found 6 with apical tuberculosis and Basedow's disease. In one case an attack of measles was followed by exacerbation of both tuberculosis and exophthalmic goitre.

The importance of chlorosis as a cause is not mentioned now as often as it was in the early days. In many cases the condition is the pseudochlorosis of exophthalmic goitre.

The relation of pregnancy to exophthalmic goitre is variable. Sometimes Graves' disease begins in pregnancy or in the puerperal period, or later. On the other hand, many patients with the disease improve during pregnancy and do not relapse afterward. The writer's experience leads him to think, with Charcot, that if the condition of the patient is not too serious, pregnancy is of advantage to the patient with exophthalmic goitre. Diseases of the pelvic organs in women have no definite bearing on the occurrence of exophthalmic goitre. Undeveloped sexual organs and menstrual disorders do not seem especially concerned. Hoennicke believes in a relationship between osteomalacia and Basedow's disease, which suggests an ovarian source, but this is certainly rare.

Nasal and pharyngeal abnormalities have been supposed to be responsible for some cases of exophthalmic goitre, but the relations are far from clear. The same may be said of floating kidney.

Many writers, notably W. H. Thompson and W. P. Sawyer, have called attention to the frequency of gastro-intestinal disturbances. These may undoubtedly explain the onset of some, but certainly not of all, cases. Enteroptosis seems less common in patients with exophthalmic goitre than in others.

From the action of iodine in bringing out latent symptoms in patients with exophthalmic goitre, not only iodine, but other chemical substances have been supposed to be occasional causes of the disease, but nothing positive is known about them.

From the study of the etiological factors it seems certain that these vary much in mode of action. Some, such as sex, must be purely predisposing. Others, like shocks and worry, may act by rousing a latent disease (possibly of exciting it without latency), while others, such as infection, seem to be capable of bringing it on more directly. It seems most probable the causes are many and various. Perhaps the mechanism is not always the same. Sometimes there may be a nervous stimulation of the thyroid gland, sometimes a stimulation by toxic, infectious, or metabolic substances. If, in addition to these variations of the process in the thyroid, we include reflex or chemical irritation of other glands, ductless, sexual, and others, and the varying influence of excretory poisons, we have no difficulty in explaining, theoretically, all the varieties of the disease. However, the diagnostic and therapeutic relations are much more deserving of attention than theories that cannot at present be put to the test.

Pathology.—So long as the functions of the thyroid were wholly unknown it was obviously impossible to formulate a final theory of a disease in which that gland was evidently affected. All the early theories were based upon the individual interpretation of the prevailing view of pathology. Parry and Graves, observers rather than theorists, were both struck by the nervous symptoms. Parry also said that he had "the notion of some connection between the malady of the heart and the bronchocele"—a notion he suggested to two other medical men. Graves described his cases in a chapter on

"Functional Diseases of the Heart." Von Basedow, in the spirit of the humoral pathology, at first looked on the disease as the result of a dyscrasia, but in 1848 he added anæmia to the dyscrasia. This view was widely held up to 1860 or later, but lost adherents under the vigorous opposition of Trousseau, von Graefe, and others. Stokes advocated a cardiac theory, but had few followers. A more popular theory was that which explained the disease by a lesion of the sympathetic nerves. Begun by Koeben (1855), and aided by the celebrated experiments of Claude Bernard and by the clinical conclusions of numerous observers, this theory long had adherents. In time it became clear that it was inadequate. The sympathetic was found normal in exophthalmic goitre, or altered without symptoms of that disease.

After the possibility of a participation by the vagus was advanced by Gros (1864) its advantages were perceived, and Sattler combined this with the sympathetic theory. Even then there were many single symptoms that could not be explained, and the medullary origin of the process naturally attracted many. Numerous experiments were made to imitate various symptoms, and in a few cases the discovery of trifling lesions in the medulla, the floor of the fourth ventricle, or restiform bodies was thought to add to the knowledge of the disease, but still left some of the most important symptoms unexplained, such as the tremor, and the psychic, nervous, and trophic alterations. A more widespread nervous alteration, such as was included in the word neurosis, was easy to admit in many cases, but something else was required to explain the varying manifestations of such an intangible state.

These facts gave impetus to the thyrogenic theory suggested by G. Gauthier in 1886, but most clearly stated by Moebius in the same year. Growing knowledge of the results of diseases of the thyroid gland (myxœdema) and the results of operative treatment of exophthalmic goitre itself and of the anatomical changes in the gland in such cases have made this theory the basis for future work. It is due the illustrious author to quote freely from his latest conclusions. Moebius[1] says: "Basedow's disease is an intoxication due to the morbid function of the thyroid gland. . . . If it is true that toxic substances are found in the body which are neutralized by the thyroid secretion in the circulation or in the gland itself, Basedow's disease can be looked upon as a 'hyperthyroidization.' . . . A priori, a normal thyroid, by relative excess due to a diminished amount of metabolic poisons to neutralize, may cause the symptoms of Basedow's disease, but there are no facts to prove this. . . . Everything points to a primary disease of the gland, but in this case we must assume more than a hyperthyroidization, that causes not only too much, but also poor secretion." Moebius abstained from a discussion on this part of the question, on the ground that it was "music of the future," but insisted on the existence of thyroid disease in all cases of Basedow's disease. "But not any or all thyroid disease, rather a peculiar alteration that can occur alone, or in association with other diseases."

Moebius recognized that all forms of goitre may be combined with Basedow's disease. "A thyroid already diseased more readily undergoes other changes. . . . More difficult is it to explain cases in which a previously healthy gland undergoes Basedow degeneration. . . . It is imaginable

[1] *Loc. cit.*, p. 7.

that chemical processes, set up by emotional disturbances, affect the function of the gland, although in such cases there was probably a disease of the gland that was not able to reveal itself until the shock came. . . . So, overexertion, 'cold,' and other general processes may be looked upon as causal." Moebius admitted the probability of a congenital predisposition, and also the influence of puberty, chlorosis, pregnancy and confinement, and infectious diseases, as factors.

The morbid product of the exophthalmic form of goitre, Moebius asserted, acts upon the heart and vessels, the central nervous system, and the skin. The exophthalmos he ascribed to a local alteration of the bloodvessels. The effect of the poison, like that of other poisons on the nervous system, is a selective one. Besides the cortex, certain nuclear regions are often affected. "The action of the poison is characterized by inhibition of function for long periods, without degeneration." Some of the skin alterations, as well as the affections of the bowels and kidneys, he looked upon as excretory.

"As the Basedowian changes in the thyroid may be due to different causes, and occur in different degrees, so all imaginable variations in course and severity occur"—acute and chronic cases, remissions and exacerbations, death, or almost complete recovery. Besides the cases crowded with symptoms, are the "incomplete" ones, with very few, so that there is no sharp line between health and Basedow's disease. Atrophy of the gland may be added to the characteristic change; myxœdema may be associated with or follow Basedow's disease.

Some of the facts bearing on the thyroid theory deserve fuller consideration. The antithesis to myxœdema need not be described at length. In the words of Moebius: "In myxœdema the thyroid is small, in Basedow's disease large; in the former the circulation is sluggish, in the latter accelerated; in the former the skin is cold, dry, and thickened (with mucin), in the latter thin, warm, and with unusual sweating; in the former the mind is sluggish, in the latter weak and irritable." The enlargement of the thyroid will have to be considered separately, and in the same place the important facts regarding the histology of the goitre in Graves' disease will be described.

The symptoms due to large doses of thyroid substance have often been described. They resemble some of the most frequent symptoms of Graves' disease, but in the majority of cases there is no exophthalmos. This symptom, however, was present in a case reported by von Notthafft[1] in 1898. In that case, a man, aged forty-three years, without neurotic antecedents, took about 1000 five-grain thyroid tablets for obesity in six weeks. By the third week he had thyroid enlargement of about 3 cm. Dyspnœa, palpitation of the heart with bounding carotid arteries, depression, and mental excitement with insomnia followed. A warm skin, moderate exophthalmos, and tremor were present, but the thyroid, although distinctly enlarged, was free from thrill and murmur. The pulse was 120, the apex of the heart forcible and displaced outward. Stellwag's and Graefe's signs were present. There was glycosuria. Recovery followed rather rapidly when the medication was discontinued, but the exophthalmos and lid signs persisted for six months. Exophthalmos has also been observed in experiments with thyroid juice (Kraus and Friedenthal) and thyroidin (Hoennicke).

[1] *Centralbl. f. inn. Med.*, 1898, No. 15.

There is a close resemblance in the metabolic changes following excessive ingestion of thyroid preparations and those of exophthalmic goitre. Mathes had a patient successfully operated upon. Afterward, on feeding him with his own dried thyroid, there was a characteristic increase of nitrogenous metabolism, with return of the symptoms. Reid Hunt's experiments seem to show an increase of thyroid secretion in the blood in exophthalmic goitre. He suggests that not only is there excessive secretion, but also diminished power in the blood to destroy it. The surgical treatment of the disease not only gives a remarkable record of improvement, but the immediate effect of the operation is often unfavorable, suggestive of an acute intoxication from the contents of the gland, accidentally admitted to the circulation.

While Moebius adhered to the possibility of a dysthyroidization, an intoxication by qualitatively abnormal secretion, this is not believed to be necessary by many others. Hoennicke was able to relieve the symptoms of hypothyroidism with thyroidin from an exophthalmic goitre. This, however, does not seem conclusive. Oswald suggests hypersecretion of an imperfect product. It seems highly probable that the divergent beliefs may be explained in time by finding that various anomalies of thyroid secretion may lead to symptoms of exophthalmic goitre. Perhaps the variable clinical picture depends partly on that, partly upon changes in other organs.

The Thyroid Gland.—For a long time after the discovery of exophthalmic goitre it was supposed there was nothing characteristic in the histology of the thyroid gland in that disease. In so-called primary cases it was thought there was a vascular change at first, followed by the alterations of simple goitre. This belief was fostered by the fact, often observed, that exophthalmic goitre frequently occurs in subjects of simple goitre, that opportunity was rarely given for the examination of the early changes, and that post-mortem examination of long-standing cases was likely to be impressed by accidental or secondary changes. More complete examinations, and especially the examination of glands removed by operations in different stages and in various classes of cases, have brought about a belief in the existence of a distinct and to a certain extent specific alteration. This view was first advanced by W. S. Greenfield (1893), and has been confirmed by many others, especially Renaut, Waehner, Edmunds, Farner, L. R. Mueller, Hirschlaff, Dinkler, Haemig, Ehrich, Lubarsch, Hansemann,[1] W. G. MacCallum,[2] Lewis,[3] Ewing,[4] and Wilson.[5] A. Kocher and also Reinbach (Mikulicz's clinic) doubt the specific nature of the changes, but while there are still many obscure details, the existence of a series of changes of a specific character seems beyond question. The essential changes are increase of parenchyma and stroma with disappearance of colloid. The hyperplasia, however, is not normal. The epithelial cells are increased numerically, but grow in an atypical way.

Various histological classifications have been proposed, but none of them are at present satisfactory. There is a general relation between the anatomical process and the severity and stage of the clinical course, but this is not equally clear in all cases. MacCallum's[6] description is based on such

[1] *Berl. klin. Woch.*, October 30, 1905, Festnummer, p. 65.
[2] *The Johns Hopkins Hospital Bulletin*, 1905, xvi, No. 173.
[3] *Surgery, Gynæcology, and Obstetrics*, 1906, iii, 476.
[4] *Trans. Assoc. Amer. Phys.*, 1906, xxi, 567.
[5] *American Journal of the Medical Sciences*, December, 1908, p. 851.
[6] *Jour. Amer. Med. Assoc.*, October 5, 1907, p. 1158.

an unusual opportunity for studying the histology of the thyroid, especially in exophthalmic goitre, that I shall quote largely from his latest report: "The thyroid is enlarged, although, as a rule, not to a great size; in some cases it is not larger than the normal, or it may be actually decreased in size. At operation the superficial veins are found to be very large and easily torn and are distended with blood, so that the gland has a very congested appearance. This is not striking in the excised portion, since the vessels collapse, and on section the interior of the gland tissue is rather pale. Usually the tissue is hard and rather rigid than elastic. Its normal amber red translucence gives way to a grayish opacity, and the fresh cut surface, instead of being glairy or gelatinous in appearance, tends to be rather dry and granular. This varies with the amount of colloid material in the alveoli, and in many advanced cases the cut surface may be still moist and give off a little glutinous material. The surface of the gland is usually somewhat nodular and rough, and this is seen to be true also of the surface, in which it is found that fine strands of fibrous tissue traverse the glandular substance, separating it into lobules.

"Usually the change is diffuse throughout the whole gland, but sometimes one lobe may be much larger than the other, and in some cases the alterations described are present only in small patches here and there throughout a gland which otherwise seems normal. These foci are easily distinguished by their fine grain and by their opacity from the adjacent colloid holding tissue.

"Microscopically there is found the change which appears in experimental compensatory hypertrophy (such as Horsley and Halsted found in partial thyroidectomy). Strands of fibrous tissue run in every direction like scars through the gland and separate the tissue into lobular masses, and in these lobules the alveoli are often separated by a fibrous tissue stroma much more abundant than in the normal gland. The alveoli are no longer rounded, full of colloid, and lined with low, cubical epithelium, but are extremely irregular in size and in form. As a rule, most of them are smaller than normal, while in the central part of each small lobule there are larger alveoli of very irregular outline, sending out diverticuli in every direction and encroached on by epithelial projections which extend into their lumen. With some special methods of staining the connective tissue it may often be made clear that such a small lobule is probably a sort of colony in which the smaller peripheral alveoli are derived from the more centrally placed, or are actually merely sections of the diverticula of the central ramifying alveolus. This alternation of large, irregular alveoli with small ones ranged around them is very characteristic, and evidently results, in part at least, from the separation of portions of the central cavity in the form of new alveoli.

"The epithelium becomes columnar not only in the large alveoli, but in the small ones as well, and thus occupies so much space that there is but little lumen left. Indeed, the areas occupied by the small alveoli may appear almost solid, so small are their cavities and so scant the colloid. In most instances the epithelium is very regular in its form throughout, and the details of its structure can be made out very clearly. The cells are plump, with a finely granular protoplasm and a sharp outline. The free surface is very sharply marked and is sometimes slightly dome-shaped. The nucleus may lie near the base or near the free end of the cell. Mitotic figures are

frequently to be found. Occasionally some of the cells appear narrow and shrunken and biconcave in form, with a very deeply stained nucleus and dark red protoplasm. These are the so-called colloid cells of Langendorff, thought by him to be especially concerned in the secretion of colloid, but which seem rather more like the result of some degenerative process. Only rarely could the so-called *Schmelzepithel* of Huerthle be seen, and then it seemed obvious that it was the effect of mechanical dislodgment and disarrangement of the cells. Similarly the extensive desquamation of the epithelial cells which one so often sees in specimens removed at operation seems to be due to the considerable pinching and handling through which the specimen unavoidably passes during the operation. Nevertheless, we have met with one or two cases in which, in association with especially severe symptoms, there has been found widespread desquamation of the epithelium, probably not the result of pinching the gland, and this is regarded by some, especially by Dr. Bloodgood, as a feature associated particularly with very severe symptoms.

"In these extreme cases peculiar alterations of the epithelial cells are sometimes found. In several instances we have observed areas in which the epithelium was enormously swollen so as to practically obliterate the lumen of the alveolus. These large, irregular cells no longer preserve the columnar form, but are shapeless masses of finely granular protoplasm which takes an intense pink stain with eosin and in which the nuclei are also irregular in form and size and stain very deeply, almost black, with hematoxylin. Usually one or two alveoli only show such a change in their epithelium, or there may be only a few cells of this form intercalated among others of the usual type in the alveolar wall, but sometimes over considerable areas all the alveoli are packed with such cells. Their significance is far from clear. Much more frequently there are found cells among the ordinary epithelial cells of the alveolar wall which are greatly enlarged, but the protoplasm of which retains the characters seen in the rest of the cells and contains only a scant basophilic granulation. The nuclei of such cells are usually much enlarged and vesicular, with scattered chromatin granules.

"The colloid varies greatly in different cases, but it seems that in most of the more severe cases it is markedly diminished in amount and altered in quality, the normal hyaline material being replaced by a very palely staining substance or by a ragged, shreddy, granular, or vacuolated mass which has no longer the refractive qualities of the normal colloid. There are some cases, however, in which there is a great deal of fairly normal looking colloid, and this is especially true of those instances in which the hypertrophy of the epithelium is relatively slight; cases, that is, in which the process is apparently advanced, at least so far as the thyroid is concerned. On the other hand, when the colloid is greatly diminished one rarely fails to find severe symptoms, and when the symptoms are very indefinite or in part absent it is usual to find a good deal of colloid.

"The most interesting cases are those in which intense symptoms exist, but in which at the same time the alveoli contain a large amount of colloid. There are at least twelve of these cases in our series, and although in some of them one may explain the existence of such large alveoli full of colloid, on the idea that the exophthalmic symptoms are associated with changes which have appeared in a gland already the seat of alterations such as are

seen in a colloid goitre, still there remain many in which there is no evidence of such a previous goitrous change. From this it appears that the presence of quite abundant colloid is not inconsistent with the development of intense symptoms, although in most cases in which the symptoms are intense the colloid tends to disappear with the advance in the alterations in the gland. It is not improbable that the amount of colloid may bear a fairly constant relation to the stage of progress of the disease, and light may be thrown on this by the consideration of the tissues removed at successive operations. One can distinguish, however, different types of change in the thyroid in different cases, for while in one group the alveoli are not larger than normal, show elevation and folding of the epithelium, and are full of colloid, another group with quite as intense symptoms will present thyroid tissue composed of very large alveoli full of colloid in which, nevertheless, the folding of the epithelial layer is most complicated. A third group comprises cases usually milder in their course in which the alveoli are large and full of colloid, but in which the alveolar epithelium is almost flat, except in certain foci or in portions of some of the alveolar walls, where it becomes cylindrical and thrown up into folds. Several cases in which extirpation of the thyroid was carried out with good results for the relief of indefinite symptoms, such as the combination of goitre with tremor only or with moderate tachycardia only, showed in the thyroid abundant colloid in large alveoli which are hardly at all irregular, but nevertheless in places show areas of epithelium which has become high and cylindrical and which is beginning to project prominently into the alveolar lumen.

"Finally, in a few cases in which the symptoms were reduced to nervousness or slight tremor with goitre, the excised tissue shows the normal structure or that of a circumscribed adenoma.

"The focal nature of the alterations in the thyroid is especially interesting, and may be recognized in some cases in the fresh cut surface of the gland by the opacity and granular surface of the altered areas which contrast with the surrounding tissue. Apparently this, too, represents a stage in the development of the lesion, and in most of the six cases which show it the symptoms had existed only a short time before the operation. Microscopically the altered areas are quite sharply demarcated from the rest and may involve a great number of alveoli, or be limited to very small foci, including only a few alveoli here and there.

"In sixteen cases there were found, on cutting through the thyroid, rounded, circumscribed nodules which projected above the general level and differed in consistency and general appearance from the rest of the gland. These are the adenomatous nodules which constitute a considerable proportion of ordinary goitre, and hence they are by no means peculiar nor characteristic of the changes in exophthalmic goitre. They are most commonly finely granular and opaque, occasionally flecked with yellow patches of necrosis or with hemorrhages, and on section they are seen to be composed of small, round alveoli lying quite separate from one another in an abundant loose stroma and lined with cubical epithelium. In only a few cases did the alveoli which make up such embedded nodules show the folding and other hypertrophic changes which characterize the tissue round about, but in one case in which exophthalmic symptoms were well marked these changes were limited to the tissue forming such a circumscribed nodule. In another case the hypertrophied tissue was found to form the thick lining of a cyst.

"The second type of circumscribed nodule is that which is composed of a tissue very rich in colloid and correspondingly translucent. The central part is often occupied by a cyst-like cavity filled with a greenish, glutinous fluid. Such nodules show microscopically very large alveoli more or less radially arranged and distended with colloid. The amount of fibrous tissue traversing the gland varies in different cases, sometimes occurring in coarse bands that separate the tissue into lobules, while in other cases there are, in addition, fibers which separate the individual alveoli.

"In six it was possible to study the thyroid at different stages in the progress of the disease, either in tissue removed at two different operations or at autopsy in patients who died some time after the operation. No very constant results were obtained. In four of the cases, in which the intervals between the times of obtaining the two specimens were seven months, eighteen months, forty-five days, and seventy-nine days, the tissues were practically identical in the two portions examined. In the fifth case, after a lapse of nine months, the tissue from the second operation showed that the epithelial cells had become greatly increased in height and the colloid rather more abundant. In the case in which the longest interval elapsed between the operations, two years and six months, the alveoli had changed from small, compact, almost solid masses of epithelium, with inconspicuous lumen and no colloid, to large ramifying spaces full of ragged colloid and lined with very high cylindrical epithelium."

Among the other anatomical changes that are seen in exophthalmic goitre the most striking only need be mentioned.

Lymphatic System.—In the Graves' thyroid there is a frequent appearance of lymphoid tissue in unusual quantities. It occurs in small or large masses of cells with germinal centres, scattered around in various parts of the gland. The lymphatic and hæmolymph glands in the neck are often found enlarged, especially at operation. In the lymphatic vessels near the thyroid, colloid material has often been described, but it is doubtful whether it is always true colloid. Besides the glands near the thyroid, the bronchial and mesenteric glands, as well as those in all other parts of the body, may be large. The tonsils are often large.

The *spleen* is often enlarged, but usually shows no characteristic histological change. It may be the seat of various accidental degenerations.

The *thymus* is very often enlarged, so that this fact, with the results of thymus treatment, has led to a theory of a thymus participation in the pathology of exophthalmic goitre. Hansemann has suggested that the thymus is influenced by the overacting thyroid either by direct contact of the two glands or through a group of enlarged lymphatic glands between them. The exact condition of the thymus in exophthalmic goitre is a matter that deserves the most careful attention.

Parathyroid Glands.—Although these are still believed by some to be concerned in the pathology of exophthalmic goitre, the investigations of MacCallum prove that the part is neither important nor specific.

Sympathetic System.—Much attention has been given to the sympathetic ganglia and nerves, and many cases have been described in which there was degeneration, atrophy, pigmentation, or calcification, as in one of von Basedow's cases, examined by Weber. In other cases no alterations have been found. Any that do occur are likely to be secondary.

Central Nervous System.—Atrophy, degeneration, and minute hemorrhages in various parts of the central nervous system have been described, but none of them are constant, and none of them can be brought into relation with more than a few of the numerous symptoms of the disease.

Hypophysis.—The importance of changes in the hypophysis seems to have been exaggerated. MacCallum, like some others, found no evidences of disease in one case.

Muscles.—So striking is the muscular weakness in exophthalmic goitre that it is remarkable so little has been done in the histological examination of those organs. M. Askanazy[1] has described a fatty degeneration and atrophy of the muscle fibres, affecting especially the muscles of the thorax, abdomen and pelvis, eyes, and tongue, which he considers toxic in origin.

Other changes in organs are inconstant or secondary, so far as we can see at present. The chief constant lesions are those in the thyroid, thymus, and lymphatic glands. Gowers, who was one of the first to observe the lymphatic changes, suggested a relation to lymphadenoma. So long as the nature of the latter is obscure, it seems simpler to look upon the lymphatic enlargements as due to irritation of a specific or non-specific kind, if it is not, as seems true in some cases, a complication of independent origin.

Morbid Chemistry of the Thyroid Gland in Exophthalmic Goitre.—*Iodine.*—All who have investigated the thyroid gland chemically in exophthalmic goitre agree that the iodine is generally absolutely less than normal. Sometimes the reduction is so great that the gland is said to be iodine-free. In other cases it may be normal (2 to 9 mg. per gland) or may be increased. Caro[2] found 10 mg. in a case in which iodine had not been taken medicinally, while Oswald[3] found 35 mg. Two facts must be borne in mind in this connection: (1) The iodine depends on the colloid, in general, and a Basedow goitre may contain considerable colloid, as has been mentioned. (2) The richness in iodine is not the only factor as an evidence of function. More important is the question whether and how rapidly the secretion enters the circulation. In the iodine-poor secretion of a hyperplastic gland the circulation can freely carry away iodine; in the colloid areas it may remain fixed.

Symptoms.—The symptoms occur in great variety, and in many combinations and varying sequences. It seems better, therefore, to describe the individual symptoms first, and then to refer to the chief varieties of type. Any classification of the symptoms at present must be artificial, and the order is followed which has the advantages and sanction of custom.

The Thyroid Gland.—The proportion of cases in which Graves' disease occurs in subjects of old simple goitre varies in different localities. In such cases the size, shape, and consistency of the thyroid differ considerably from others. The gland may be of considerable size, and unsymmetrical; may be hard or soft, cystic, adenomatous or fibrous, to a greater or less extent. It is impossible to learn in all cases whether there was a goitre before other symptoms came on. Many people have goitres of considerable size without knowing it. Sometimes the characteristic or Basedowian goitre comes on rapidly, within a few weeks, days, or even hours. It may then remain

[1] *Deut. Arch. f. klin. Med.*, 1898, Band lxi.
[2] *Berl. klin. Woch.*, 1907, p. 519.
[3] *Wien. klin. Woch.*, 1905, p. 649.

stationary, or may vary from time to time. Sometimes the exacerbation coincides with menstruation or some other process; sometimes no explanation can be given.

In some cases no enlargement can be made out by the most careful examination. From what we know of the pathological anatomy of the Basedowian thyroid, this is not remarkable. It is obvious there may be extensive alterations of the gland without enlargement, or even with a reduction of the size absolutely or as compared with the average. Clinically such cases are rare, especially in the experience of those who take pains to make careful examinations, and when repeated examinations are made. For example, Murray, in 180 cases, found goitre absent only 8 times, and in 5 of them there was a history of goitre at some time. The writer has seen only one case (one examination) in which the gland was not distinctly enlarged.

In general, the enlargement is not great. Murray makes a useful classification of size as follows: (1) Slight, when the gland can be distinctly felt, though not noticed by the patient; (2) moderate, when it can be seen and felt; (3) considerable, when it is obvious and disfiguring; (4) enormous. Most cases fall under the first two classes, about equally divided. Murray found one-sixth of considerable size, a larger proportion than many others have found. He also records a rare "enormous" goitre, in which the neck measured twenty-three inches. The enlargement had existed thirty-four years. Usually all the lobes are enlarged, including the pyramidal process if present. In many cases the enlargement of the lateral lobes is equal. In about as many the right lobe is larger, in a few the left. The surface is usually smooth in small goitres, uneven, nodular or granular, or very uneven in larger ones.

The consistency is rarely hard. More often it is firm elastic, or soft elastic, or soft. Sometimes it is very soft, almost like a varicocele. In many cases there is visible pulsation in the lateral lobes, sometimes transmitted from the carotids; sometimes the veins over the goitre show marked pulsation, or the whole goitre pulsates. In other cases there is palpable pulsation only. In many cases there is a more or less distinct thrill over the whole of the enlarged lateral lobe, sometimes only over the larger one if they are uneven; sometimes only at the upper poles, rarely the lower.

On auscultation there is usually a systolic murmur, sometimes a diastolic as well as systolic murmur, less frequently a continuous murmur, sometimes with systolic accentuation. It varies much in character from a soft blowing to a musical twang or squeak, called by Fuller the sleigh-runner murmur. According to P. Guttmann, who first called attention to the diagnostic importance of the murmur, the systolic part is arterial, due to hypertrophy of the left ventricle and the uneven dilatation of the arteries in the gland; the diastolic murmur is venous and anæmic. The vascular phenomena may be present when the thyroid is apparently not enlarged. Murmurs may be absent for shorter or longer periods. They do not depend upon the propagation of heart murmurs.

In general the enlarged thyroid of Graves disease is not painful or tender, but may be so in the beginning or during temporary increase of size. The goitre rarely causes pressure symptoms, but when the disease is added to an old goitre there may be pressure on the trachea or nerves, and the symptoms vary according to the size of the goitre.

PLATE I



Exophthalmic Goitre.

Circulatory Phenomena.—Patients rarely fail to notice changes in the rate and rhythm of the heart-beat, and in many cases palpitation or frequent pulse is mentioned as the earliest symptom. At first "palpitation" is noticed only after exertion or excitement, and is then important only when it is unusual for that patient. Sometimes it is associated with a feeling of suffocation, or swelling in the throat. Graves thought the well-known globus hystericus might be due to sudden swelling of the thyroid. It is suggestive when palpitation occurs in persons who have no discoverable cause. Much more constant and important, by the time patients come under observation, is frequent pulse, tachycardia,[1] which may exist without the patient knowing it. This varies from 90 to 120 or 140 to the minute, but at times may reach much higher rates—225 in one of the writer's patients—for many hours. In the rare cases without frequent pulse—60 to 80, as in two of the writer's (male) patients—it is possible the normal pulse was still lower. The tachycardia usually shows a close relation to changes in the severity of the disease. Even in fairly constant improvement the pulse is likely to be higher than would be expected from the age and condition of the patient.

The cardiovascular phenomena are universally admitted to be thyrogenic, but their exact origin is unknown. It is obviously not mechanical. Although tachycardia can sometimes be brought out by ingestion of thyroid preparations, and although Pfeiffer[2] saw frequent pulse in dogs after administration of human thyroid secretion, Paessler and Schultze[3] had negative results. Such experiments obviously do not imitate the process in exophthalmic goitre, and until the mechanism of acceleration and depression of the heart and the qualities of thyroid secretions are better understood, speculation is not likely to add much to our knowledge.[4]

Postmortem the heart usually shows hypertrophy, especially of the left, sometimes the right (Fr. Müller), ventricle, with dilatation, and with relative insufficiency of the valves. Endocarditis, also arteriosclerosis, may be associated. The enlargement of the vessels in the thyroid does not show, as a rule, after death, but the thyroid arteries may be relatively more sclerotic or their walls may be attenuated.

Clinically the precordium is often prominent, especially when the disease begins in early life, and the whole heart area, or the whole anterior wall of the chest, may be made to heave with the forcible action of the heart. This may be perceptible through the clothing. On palpation it can be felt as an unusually violent impact—"pounding." Sometimes there is a systolic thrill or a diastolic shock. With this the apex beat may not be much displaced, or even if too far out, as the nipple-line, it may be in the fifth, or even the fourth interspace. The dulness is increased, especially to the left. On auscultation the sounds are usually loud, but the first sound is rarely clear. The sounds may be audible at a distance. Murmurs are common, especially at the apex, conducted into the axilla; sometimes the same or a different murmur is audible over the base. Diastolic murmurs in the aortic area are sometimes present. Sometimes the murmurs are audible over the

[1] Although not so accurate etymologically, "tachycardia" has the force of custom, and so is preferable to such terms as "pycnocardia," "polycardia," or "sychnosphyxia."

[2] *Wien. med. Woch.*, 1907, p. 1173.

[3] *Mitth. a. d. Grenzgeb.*, 1905, Band xiv, p. 330; *ibid.*, 1907, xvii, 655.

[4] See Minnich, *Das Kropfherz*, 1904; Discussion, *Congress f. inn. Med.*, 1906.

whole thorax or in the extremities. The causes of the murmurs are undoubtedly various. Probably muscular insufficiency is the chief factor, anæmia a rare one. Valvular disease of endocarditic origin is sometimes associated, as it probably was in Parry's first patient, with a history of rheumatism. Reduplication of the sounds and gallop rhythm are sometimes present. Arhythmia will be mentioned below. Stenocardia, even typical angina pectoris, has been observed, but may be a complication.

The vascular anomalies are even more striking than the cardiac ones. The carotids alone may be involved, or those of the head (retinal arteries), or the head and body may be shaken at each heart beat, as in some cases of aortic regurgitation (sometimes called "Musset's sign," after Paul de Musset, who described it in the case of his brother, the poet[1]). Capillary or even venous pulse (liver pulse, splenic pulse) may be present. Pulsation of the abdominal aorta is often annoying to patients with Graves' disease. The radial pulse is variable. Sometimes it is small and soft, sometimes small and hard, sometimes large. It is likely to be quick (celer), even when it feels hard, and this is borne out by sphygmographic tracings. The blood-pressure (systolic) is sometimes normal, sometimes low, but often high, even when the rate is not extremely high (P. Marie, Spiethoff, Donath, Morris and Edmunds, Dock[2]). The widespread view that the pressure is low is doubtless due to the quick pulse, which in turn depends upon a large pulse pressure. As T. C. Janeway points out, diastolic determinations are difficult to make, and all the factors are greatly modified by accidental causes, such as emotional excitement.

Arhythmia is not uncommon, but in most cases is merely an intermission of the radial pulse at longer or shorter intervals, from (ventricular, usually) extrasystole. Sometimes the extrasystole occurs at a certain phase of respiration. In other cases there are more ma ked arhythmias. There may be auriculoventricular arhythmia, with auricles and ventricles contracting simultaneously at certain periods and with visible, palpable (shock), and audible signs (extraordinarily loud tone) over the veins of the neck at those periods. Occasionally there is alternating pulse, with slight or marked disproportion of the beats. Sometimes the alternation is due to regular extrasystoles, and may then be mistaken for a dicrotic pulse and the pulse rate taken to be half what it really is. In other cases there is irregularity of force and rhythm, again leading to too low pulse count. The slight or regular arhythmias are of no special significance. The severe ones are usually of serious omen, as pointed out by von Graefe (1867), but some patients have been observed to have irregular pulse for many years without evidence of cardiac failure. In such cases tracings should be made, in order to enable us to learn whether there is any rule. Serious irregularity coming on early may be recovered from; later, with degeneration or insufficiency of the heart, it is less amenable to treatment.

Erythema will be mentioned later. Hemorrhages sometimes occur from the nose, lungs, stomach, or skin. In some cases bedsores develop rapidly. Œdema will be mentioned below (skin). In rare cases gangrene, especially of the legs, has been observed.

Eyes.—Protrusion of the eyes was noted by Parry in his first case, and for a time formed one of the "symptomatic tripod" with goitre and palpitation of

[1] Zeitner, *Wien. klin. Woch.*, 1905, p. 483.
[2] *American Medicine*, February 24, 1906, p. 271.

the heart. More extensive observation soon made it clear that exophthalmos, like the other signs, could be absent. It comes on comparatively late, and is present only in two-thirds to three-fourths of all cases. It varies much in degree, from a slight prominence of the eyeballs, that can only be recognized by one who carefully observed the eyes before, up to veritable goggle-eyes (Glotzaugen), or so that the bulbs actually slip past the eyelids. Usually the exophthalmos is just enough to prevent complete closing of the lids. The degree bears no relation to the size of the goitre or the severity of the other symptoms. In many cases (one-seventh, Wilbrand and Saenger) the exophthalmos is unilateral, or is larger on one side. In the former case the other eye may become affected later. In one case (Yeo) there was goitre on one side and exophthalmos on the other. The protrusion may come on in a few days, but usually does so slowly, sometimes irregularly. In the early stages the swelling can be reduced by gentle pressure, but later this cannot be done. The cause and mechanism of the exophthalmos are still unknown. Postmortem an increase of orbital fat has often been noted, but the rapid protrusion in some cases proves that such a condition is not primary. Vascular congestion and œdema have been assumed. The latter is often present, with œdema in the folds between the lids and the edges of the orbit. Besides these causes, spasm of the orbital muscle of Müller, with or without weakness of the orbicularis, has been suggested. Experiments of MacCallum and Cornell[1] make it probable that this does play a part. Landström has recently described a cylindrical band of smooth muscle fibers, surrounding the point of the eye, rising from the orbital septum and inserted into the equator bulbi, leaving an opening for the levator palpebræ superioris. He thinks this muscle can account for Moebius' sign, as well as the other ocular symptoms.[2] Hyperthyroidism, however it may act, seems to be the cause of the exophthalmos. Besides the cases of hyperthyroidism by treatment, experimental proof has been brought by Hoennicke.[3] He used normal thyroidin, so that it seems unnecessary to assume dysthyroidization, so far as exophthalmos is concerned. Its production takes time, and requires a predisposition as well as a certain relation between the bony orbit and the bulb. Fr. Müller points out the probability of some action of the thyroid upon the sympathetic. In two cases of unilateral exophthalmos there was goitre on the same side. In one of the two the goitre had been bilateral, and also the exophthalmos. After one side of the thyroid was removed, the exophthalmos disappeared on that side.

Exophthalmos is, of course, not peculiar to Graves' disease. Besides aneurisms, inflammation and tumors in the orbit, it is sometimes present in cases of atheroma with dilatation of the arteries and in chronic cyanosis of the head. Marina saw it in a patient with gout and aneurism of the basilar arteries, with dilatation of the cerebral vessels in all parts. Fr. Müller points to its occurrence in some cases of lead poisoning as a toxic vasomotor condition.

Exophthalmos is rarely an early sign of Graves' disease. From the beginning numerous observers mentioned a peculiar lustrous appearance,

[1] *The Medical News*, October 14, 1904.

[2] *Ueber Morbus Basedowii, Habilitationsschrift:* also *Münch. med. Woch.*, March 31, 1908, p. 689.

[3] *Verhandlungen des Congresses f. inn. Med.*, 1906.

or a staring of the eyes. The staring, with a diminished frequency of reflex winking, is now known by the name of Stellwag's sign. Dalrymple, according to W. W. Cooper (1849), explained the cause of the appearance, as we do now, to spasm of the levator palpebræ superioris, but Cooper thought the spasm was not peculiar to the disease, and it remained for Stellwag (1869) to show not only its mechanism, but its clinical value. The appearance is due to an exaggeration of that seen when the gaze is fixed, especially as in fright, showing sclera above the cornea, and giving the appearance of a glass eye. It occurs early, is rarely absent, varies from day to day in its degree, and sometimes is more distinct on one side. Stellwag's sign is not peculiar to exophthalmic goitre. Besides fright, it occurs in maniacal conditions, in hysteria, tabes, and pregnancy. It is related to the lessened frequency and completeness of winking, although the two symptoms do not always coincide. Many patients with Graves' disease wink as often as normal persons. Its explanation is generally found in a higher excitation of the nerves.

Graefe's sign consists in the loss of agreement between the motion of the lids and the raising or lowering of the plane of vision. It is seen especially when the patient looks from above downward. The upper lid then falls more slowly or even jerks back. The sign cannot be seen so well in the lower lid, although if the patient looks up, the jerking of the upper lid can also be seen, sometimes, in that motion. Graefe's sign is not always present, nor at all times in cases where it does occur. Authors differ much in their observations. The writer found it in about half the cases, as did Lewin (55.5 per cent.), varying much at different times. Griffith found it in 13, Paessler in 14, and West in 17.6 per cent. of cases only. It is generally present on both sides. Graefe's sign is sometimes present in healthy people; Raymond found it in Thomsen's disease. It is sometimes present with ptosis. Wilbrand and Saenger,[1] who discuss the matter fully, give five theories of the cause of the symptoms, viz., sympathetic; central; action of orbital vessels upon the levator; insufficiency of the orbicularis; increase of the forces that cause elevation. It is important to note that other evidences of sympathetic irritation (dilatation of pupils) are rarely present, and the authors cited believe there is either muscular irritation or mechanical relations with the exophthalmos. Ptosis sometimes occurs, but usually without evidence of sympathetic disease.

Another sign connected with the eyes is that described by Moebius, and called after him by Charcot. In this, if the patient fixes his eyes on the tip of his nose, or better, an object on the level of his eyes and near them, one eye turns out. There is no diplopia with this. Some patients complain of fatigue in the eyes at the time, others do not. It does not depend upon exophthalmos, but may be favored by that. The sign is of relative value only. It occurs in many myasthenic conditions.

As to other symptoms on the part of the eyes and their appendages, severe exophthalmos is often associated with pain and subjective tension in the eyes; milder cases are usually free from pain and other sensations. The lids are often dark and sometimes swollen; the bulbs are glistening, sometimes there is excessive secretion of tears. From the diminished motion of the lids and the lessened sensitiveness of the cornea, ulceration is

[1] *Die Neurologie des Auges*, Band i, p. 45.

favored. The pupils rarely show alterations, aside from accidental conditions. Mydriasis and miosis sometimes occur, with other symptoms of irritation of the sympathetic. This cannot, as a rule, be ascribed to pressure, but seems to be due to toxic processes.

Narrowing of the fields of vision has been noted, but Moebius considers it the result of an associated hysteria. Amblyopia, achromatopsia, paralysis of various ocular muscles have been described, rather as complications, however, than as part of the main disease. Tremor of the bulbs has been described in rare cases, also tremor of the eyelids on attempts at closing them.

Ulceration of the cornea, observed in one case by von Basedow, is a rare and dangerous occurrence. Von Graefe thought it more common in men in advanced age, and Jessop found 7 men affected to 18 women (instead of 1 to 4 to 10). It occurs in some patients apparently not severely ill. Cataract operations are said to be badly borne by patients with Graves' disease. Circumscribed œdema, ephemeral or periodic, pigmentation of the skin, and also vitiligo, may occur on or near the eyelids.

Nervous System.—The nervous system in Graves' disease is always abnormal, and in many patients it is the seat of the earliest symptoms. This is spoken of as "nervousness," and on closer inquiry appears often as mental irritability, excitability, or restlessness. Sometimes neurasthenic conditions can be traced back long before Graves' symptoms, either as irritability or mental fatigue from trifling causes, with loss of memory and intolerance of company or of strangers. Some patients are depressed, apprehensive, or have morbid fears, even dread of death. Others have morbid exaltation, with capacity for considerable mental labor. The mental condition is sometimes well described by the expression "chorea of ideas." Murray mentions a patient who learned Turkish, and the writer has known several who finished courses in medicine in the usual time. Severe mental alterations may occur. True psychoses are rare, but Basedow's first two patients were considered demented. Depression and exaltation occur and may alternate. One patient of the writer's acted like a person in mild cheerful alcoholic inebriety. In severe acute cases there may be stupor or mania, with confusion of ideas and hallucinations, either visual or auditory. Delirium of persecution and grandeur occur, also suicidal and homicidal mania. Recovery is possible, but the outlook is generally grave. In less severe cases there are various paræsthesias, such as globus, throbbing, vertigo, and formication. In one case the writer saw temporary paraphasia. The sensation of heat may be complained of when the skin is not red or warm. Loss of sleep is often complained of, and really exists in a large number of cases. Dizziness and faintness are not rare. Headache does not seem to be very common. Neuralgias sometimes occur in various parts of the body. Local twitching may be annoying, and also cramp, especially in the legs, at night. The tendon reflexes are not rarely increased, and spastic phenomena sometimes occur. Epilepsy has often been reported, but is, of course, only a complication. Ascending paralysis and multiple neuritis have also been observed.

Muscles.—A characteristic symptom of Graves' disease is tremor, mentioned by previous authors, especially Charcot, and fully investigated by P. Marie (1883). It varies much in force, from a fine, barely perceptible tremor up to a distinct shaking of extremities, head, or the whole body. When mild it is best seen in the hand and fingers when outstretched, or in movements

like sewing or drawing a straight line with pen or pencil. By having the patient draw a line slowly in a measured time, a useful record of the tremor may be obtained. The tremor is rapid and rhythmic, 8 to 10 in a second. It occurs in almost all cases, but is sometimes temporarily absent. Choreic movements occur sometimes. Mackenzie reports a rare case of tetany-like movement.

Muscular weakness is another very characteristic symptom. It is so rarely absent that it is strange that Askanazy's finding of muscular atrophy and degeneration has not been more widely controlled. Fr. Müller gives some comparative measurements showing the degree of the weakness.

	Basedow's Disease.		Normal Woman.	
	R.	L.	R.	L.
	Kilogram.		Kilogram.	
Shoulder, adduction	3.8	3.6	13	12
Shoulder, abduction	1.9	1.5	15	12
Elbow, flexion	4.8	4.0	30	25
Elbow, extension	5.6	4.8	18	14
Finger, flexion	6.5	5.5	20	18
Hip-joint, flexion	4.6	4.1	30	
Hip-joint, extension	5.1	4.6	35	
Hip-joint, adduction	4.5	4.5	15	
Hip-joint, abduction	4.0	4.0	15	
Knee, flexion	7.1	6.6	30	
Knee, extension	13.4	12.1	40	

Paralysis and even atrophy of certain muscles, such as those of the neck, arms, hand, and peroneal group, have been observed. It is probable the nervous relations of the paralysis differ in various cases, sometimes being central (optic nucleus in the case of eye muscles); in others the process is purely muscular.

A striking but comparatively rare sign is giving way of the legs (Charcot), but weakness of the legs noticed in walking or climbing stairs is very often mentioned early. It can go on to paraplegia, without bladder symptoms, loss of sensation, or marked atrophy, but with loss of skin and patellar reflexes. A similar condition has been seen in myxœdema (Mackenzie, Revilliod). Hemiplegia and monoplegia have been described. In many cases with nervous complications the relations have been very obscure. In such cases the diagnosis of Graves' disease has been made when the symptoms were confused beyond accurate recognition. Tachycardia and tremor in moribund patients are not necessarily signs of the disease, even if an old goitre is present.

The Skin.—The skin shows many and various changes. It is usually warm and moist. The warm skin is usually associated with a feeling of subjective warmth and a tendency to feel better in cold weather. Sweating is sometimes excessive, especially under excitement. In the case of a teacher, the writer has seen pools of water form from the perspiration falling from his hands during a recitation. Partly from the moisture, partly perhaps from an atrophy of the skin, the resistance to the galvanic current is lessened (Chvostek, Vigouroux), but this is of no special diagnostic value. Dryness of the skin is suggestive of myxœdematous degeneration.

The skin of the exophthalmic goitre patient is often pale, even when the hæmoglobin is not notably reduced. Some look normal, others have a

more or less constant flush of the face and sometimes the neck. On examination of the thorax a diffuse mottled blush is often seen, usually fading soon, but easily brought on by touch or by embarrassment. Various degrees of vasomotor anomaly are shown by rubbing or scratching the skin up to striking and lasting dermographism and urticaria. Pruritus is sometimes present. Circumscribed œdema is not uncommon, and may be ephemeral or periodical, or last a long time. Œdema of the extremities occurs often and in varying degrees. It is sometimes of high degree, and of unusually solid consistency. In one case it extended up to the body, during a period of severe symptoms, but disappeared with improvement of the other symptoms. Ascites occurs occasionally.

Vitiligo is sometimes present. A more common pigment anomaly is a brownish discoloration, from pale to dark, like sunburn, or the diffuse pigmentation of Addison's disease. It is usually more intense on the face and in places normally pigmented, or where pressure is caused by clothing. The mucosa is rarely affected. The pigmentation often fades as the other symptoms improve. Sometimes scattered areas of dark color appear on the skin. Many observers have described pigmentation of the eyelids, but it is neither constant nor early, and hardly deserves to carry the name of any of those who have mentioned it. In one case with pigmentation von Schrötter also saw lipomatosis of the lower extremities. Scleroderma has often been observed in patients with Basedow's disease. Alopecia is not uncommon. David Walsh[1] finds a band of baldness across the frontal region with a "bay" running back from each end, often described as a "high forehead," associated with a tendency to exophthalmic goitre. The writer believes the condition more suggestive of hypothyroidism. The eyelashes and eyebrows are also sometimes lost, adding to the strangeness of the patient's appearance. In one of the writer's patients the body hair all fell out with unusual rapidity under *x*-ray treatment. Others have noted spontaneous loss of body hair. Early graying of the hair is said to occur.

The Lymphatic Glands.—The lymphatic glands near the thyroid are always found enlarged at operation. In many cases the superficial cervical glands are palpably enlarged, and in a small proportion the axillary and inguinal glands also.

The Spleen.—The spleen is often enlarged. The enlargement of the thymus, so often noted at autopsies, is rarely discovered clinically. Careful examinations should be made in every case by percussion, palpation, and, if possible, the *x*-rays.

The Blood.—The blood does not show as marked alterations as the early reports would lead one to expect. There is often a mild simple anæmia or chlorotic anæmia. Chlorosis is sometimes present as a complication. Increase of the lymphocytes is very frequent, either relative or absolute, with decrease of polynuclears and without increase of total leukocytes. A. Kocher thinks the lymphocyte increase is proportional to the severity of the disease, but sometimes absent in severe cases. In these the prognosis is serious. In improvement from any form of treatment the leukocytes usually return to a more normal formula.

The Alimentary Canal.—There are many symptoms on the part of the alimentary canal. Anorexia is uncommon; the appetite is more often good,

[1] *Proc. Roy. Soc. of Med.*, May 1908, p. 195.

even voracious. Thirst may be increased. Attacks of vomiting sometimes occur, especially in severe cases. In the latter the vomiting may be severe and exhausting, though rarely painful. The secretory and motor functions of the stomach in mild cases are often good, but sometimes the free hydrochloric acid and pepsin are reduced, and there is premature emptying of the contents. Excess of mucus is sometimes present. Postmortem, atrophy of the gastric mucosa has been observed.[1] Diarrhœa is a common symptom occurring in about one third of the cases, sometimes in paroxysms or "crises," with or without vomiting. It may be dietetic, or may be due to gastric hyposecretion with hypermotility. Often the diarrhœa has the features of a toxic process, coming on suddenly with abdominal pain, and with watery stools to the number of five, ten, fifteen, or even forty a day. It may stop as suddenly as it began, even without treatment, or may last several days in spite of opiates, astringents, and intestinal antiseptics, with or without a preliminary purge. Sometimes the passages are choleraic, at other times bloody. They may show good digestion, or none at all. Bile coloring matter is often deficient. Between the attacks the bowels are often constipated. Moebius reports a case in which diarrhœa, headache, and insomnia were the earliest complaints, although the patient had a goitre and tachycardia. Tremor and other signs developed later.

Dyspnœa is often complained of, and can be noticed, even aside from exertion, in a considerable proportion of cases.[2] It is often associated with deficient expansion of the thorax (Bryson's sign), which may be as low as 1 to 1.5 cm. Litten's sign often gives evidences of imperfect contraction of the diaphragm. Dyspnœa and deficient expansion may most readily be explained by muscular weakness. Hofbauer and Sharp report crises of dyspnœa. In some cases the dyspnœa is partly, at least, due to pressure on the trachea, sometimes to pressure on the recurrent nerve. A dry, sometimes ringing cough, hoarseness, and aphonia may be present. Pulmonary hemorrhages have been observed.

The Kidneys.—The kidneys are rarely severely affected, but albuminuria with hyaline casts is usually present when the heart is much dilated. The urea, total nitrogen, uric acid, and phosphates are increased. In many cases alimentary glycosuria has been observed; in some, diabetes mellitus. Polyuria is not infrequent, and may often be explained by the polydipsia and large meals; in other cases it may be of nervous origin.

The Sexual Organs.—On the part of the sexual organs the changes are not, as a rule, prominent. Loss of sexual power occurs in men occasionally. Menstruation is usually in proportion to the condition of the blood and nutrition. Atrophy or hypoplasia of the uterus and ovaries is a rare occurrence. The mammary glands are usually more or less atrophic, but sometimes seem to have become larger during the disease. This may be related to the lipomatosis, sometimes present in other parts of the body. In Basedow's male patient the mammæ were swollen and hyperæmic, and secreted colostrum. Pregnancy is often beneficial to patients with exophthalmic goitre, though in general it should not be recommended unless the condition is fairly good and seeming to improve.

In some cases postmortem the bones have been found soft, and in a patient

[1] Miesowicz, *Wien. klin. Woch.*, 1904, p. 1206.
[2] See Hofbauer, *Mitth. a. d. Grenzgeb. d. Med. u. Chir.*, 1903, Band xi.

with kyphoscoliosis Koeppen made a diagnosis of osteomalacia. The same author reports dental caries. The writer has not noticed a special tendency to that, nor to the deformities of bones or (except in one case, with scleroderma) the pointed fingers described by Revilliod. Chronic and also intermittent arthritis have been described in rare cases.

Emaciation.—Emaciation is an almost constant and suggestive sign. The loss of weight is rarely less than fifteen or twenty pounds when the patient is first seen, and may be thirty or even sixty or more. In one of Mannheim's cases it was ninety-three pounds in ten months. It may amount to one-third or even half the original weight. It often begins before diarrhœa and vomiting, but these may make it much worse. Huchard has well spoken of "crises of emaciation." Sometimes there is almost as marked and rapid gain—thirty-three pounds in ten weeks in one patient, in whom sixty-two pounds had been lost in one year. The gain may take place notwithstanding diarrhœa. In mild cases there may be a gain in weight—thirty-eight pounds in two years in one patient. The emaciation is evidently due chiefly to thyroid intoxication, and this helps to explain why it varies so much in different cases.

Fever.—Although the feeling of subjective warmth, or even heat, is very common in exophthalmic goitre, actual fever is rather rare, except in the fatal cases. Bertoye,[1] who has made the most extensive investigations in this respect, finds high temperature during long or short periods, and of different degrees of severity. In some cases it resembles that of typhoid fever, and is benefited by cold baths. The other symptoms of fever are sometimes present. In the writer's experience actual fever has been rare; in fact, present only in fatal cases (in one, 107°). W. G. Thompson has seen fever of 101° to 104° F. in 14 out of 43 cases, in some above 104° F. "It is of septic type, oftenest remittent, but sometimes intermittent, and always irregular and occasionally remaining elevated three or four degrees for several consecutive days. The duration of the fever varied from a few days to several weeks. Often it lasted for ten days or a fortnight, in one case for forty days, and in another thirty-eight days." Bertoye thought the fever due to nervous and infectious causes combined. It would seem most probable that either thyroid toxæmia or secondary infection is the cause.

Complications.—In such a chronic disease as this any and all possible complications may be expected, but only the most peculiar or striking ones need be mentioned. Diseases of other ductless glands are of the greatest interest, because many of their symptoms may be present in cases of exophthalmic goitre. Among them may be mentioned acromegaly, described by Ballet and Holmgren. Myxœdema is a sequel rather than a complication, although the symptoms sometimes run parallel for a time. Chlorosis is sometimes observed; Neusser has reported a case of pernicious anæmia; pseudoleukæmia has been reported, and deserves careful investigation whenever suspected. In one such case the writer found a distinct leukæmic change in the characteristics of the lymphocytes. In Neusser's case of Basedow's disease with pernicious anæmia, atrophy of the liver was found postmortem. Jaccoud has reported a somewhat similar case, with icterus and hemorrhages and fatty degeneration of the liver. Neusser in this connection calls attention to the relation between the thyroid and the liver. Stockton and Woehnert[2] report a case of thrombosis of the superior vena cava and innominate veins.

[1] *Étude clinique sur la fièvre du goitre exophthalmique*, Lyons, 1888.
[2] *New York Medical Journal*, 1908, lxxxviii, 145.

Hysteria in all its forms may be associated with Graves' disease. Many of the cases of so-called epilepsy, perhaps also those of "chorea," belong here. Moebius, and more recently Alfred Gordon, have called attention to the combination of Graves' disease and paralysis agitans. Tabes dorsalis is often a complication, and one of special interest on account of the possibility of a syphilitic origin of the thyroid alteration. Abrahams has reported the recovery of a case of postsyphilitic Basedow's disease. L. Lévi has called attention to the frequency of Basedow's disease among tuberculous patients—13 out of 170, besides 14 incomplete cases. Arthritis is an occasional complication.

Clinical Forms.—There are various classifications of exophthalmic goitre and many are satisfactory, provided their limitations are understood. Cases are often spoken of as primary or secondary, the latter when the symptoms occur in the subject of a previous goitre, the former when the goitre develops with or after some other symptoms. But often there is a goitre unknown to a patient, or even to the physician. With greater care the goitre could often be found in such cases. All surgeons speak of the frequency with which, at operations, thyroids supposed not to be enlarged are found distinctly enlarged, and these cases can often be recognized by finding a thrill or murmur over the gland, evidence of vascular anomalies. From the anatomical and clinical standpoint there is some advantage in Kocher's classification: Vascular goitre; Basedowized goitre; Basedowian goitre. The differences are gradual. Even if in some cases there is a history of previous goitre, this does not indicate that the goitre as such causes the other symptoms, the latter are not secondary in that sense. In both primary and secondary cases the symptoms occur in the same general order, and although in the former the course is often more acute, there are many exceptions.

Acute and chronic cases are distinguished according to the length of time they last, the former ending in a few weeks or months, although some would term "acute" cases lasting a year.

According to the number of symptoms cases are spoken of as complete, incomplete, abortive, rudimentary, or fruste. The terms most often are used with reference to the chief symptoms, especially those longest known. In a disease with so many symptoms the question of completeness must depend largely upon the accuracy of the observations and the care in noting them. As at present used, we do not know in a given case of "incomplete Graves' disease" whether it lacks, *e. g.*, exophthalmos or goitre, or has none of the classic signs, but possibly has nervousness, emaciation, and tachycardia. Some further qualification would be useful in such cases. Acute cases are often apparently primary and with many symptoms. Many, if not most of these, if carefully examined will be found to have had distinct signs months or years before the acute appearance of the striking symptoms.[1] Perhaps the same is true even of the peracute cases, of which examples are found in literature, in which the symptoms come on in a few hours. From the nature of the alleged causes, overexertion, sexual excess, or excitement, as in one of von Graefe's cases, fright, etc., it seems certain some very unusual process must have been present. In some cases the onset is abrupt, but is soon followed by a rapid improvement. In the great majority of cases we can find by care-

[1] Arneill, *Journal of the American Medical Association*, 1900, xxxv, 880.

ful inquiry a long history, up to twelve or fifteen years, of some slight symptoms. Then, usually after some definite occurrence, such as shock, exertion, infection, this latent stage passes into one with one or more important symptoms. This is often followed by a relative improvement. Renaut has suggested the useful classification of a latent stage, stage of intolerance, and stage of tolerance. It is characteristic of the disease that exacerbations tend to develop rapidly but to subside slowly, and to occur at longer or shorter intervals, sometimes without, but usually with, a discoverable cause, during the existence of the disease.

The early idea that the disease was characterized by a "triad" of symptoms gives way slowly, notwithstanding the long array of symptoms that occur in general, and the number that can be observed in many cases. As has been said before, enlargement of the thyroid is often present early and almost never absent. Nervousness or tremor is almost as frequent. Heart symptoms are also rarely absent, although subjective palpitation is by no means essential. Acceleration of the heart rate, taking into account the age and constitution of the patient, is rarely missed. In cases of very infrequent pulse, as 50 to 60, it is important to know whether the heart beat is equally slow. It is possible in a Basedow's case to see a pulse of 50, 60, or 80 noted, by reason of an arhythmia of some kind. In one case, with the pulse noted as 52, there was a regular alternation due to extrasystole. Careful palpation revealed the small beat, but a tracing was necessary to prove it was a weak systole and not a dicrotic wave. In acute cases heart symptoms are usually early and severe—tachycardia, dyspnœa, and irregularity; besides these, vomiting and diarrhœa, fever, sweating, vasomotor changes in the skin, and pigmentation are very often present. Some symptoms occur only in severe cases or severe stages, *e. g.*, fever, hemorrhage, delirium, paralysis.

Diagnosis.—This is difficult only in cases with few symptoms, and especially when those are mild. Cases with slight tachycardia and mild nervous disturbance are often overlooked because a careful examination is not made. If the tachycardia does not subside in a short time with rest, if there is no ordinary heart lesion, and if there is characteristic tremor, with Stellwag's and Moebius' signs, emaciation, increased perspiration, and poor sleep, with dyspnœa on slight exertion, the diagnosis can usually be made without difficulty. In goitre districts a goitre is not in itself a valuable sign, but if there are vascular anomalies in the thyroid or over it, as described in the preceding sections, the diagnosis can be made. The diagnosis of "goitre heart" in such cases is by no means as safe or rational as that of Basedow's disease. Exophthalmos of the characteristic kind is hardly possible to refer to anything else, but cases of orbital tumor or aneurism of the orbital artery are too often mistaken for exophthalmic goitre. Careful examination of the eyes and the other symptoms cannot leave one long in doubt in such cases.

The confusion of mild cases of Graves' disease with neurasthenia cannot withstand the complete physical examination and study that every suspected patient with neurasthenia should have.

"Iodism" can be recognized by the history, but in all such cases careful investigation should be made in order to determine if the so-called iodism is not really a hyperthyroidism that needs the same kind of treatment that cases of Basedow's disease require.

Kraus suggests that determinations of the respiratory metabolism (increase

of CO_2 and N) by the use of the Zuntz-Geppert apparatus may be useful in diagnosis. Fr. Müller observes that this is too complicated, and that careful tests with iodine would be better; patients with hyperthyroidism show their intolerance by emaciation and tachycardia, even in small doses.

Prognosis.—Exophthalmic goitre has been defined as a disease from which patients never recover and never die. It would be more accurate to say that few recover and some die. Relative recovery, however, is not rare. In this the patient becomes able to carry out the usual duties. He, or more frequently she, is not perfectly well, but about as well as patients with mild neurasthenia. Many years may pass with freedom from severe symptoms, but with some nervousness, slight increase of pulse rate, and exophthalmos with Stellwag's and often other eye symptoms. More complete recovery may be expected when operative treatment is carried out early. The disease is essentially chronic, a duration of ten, twenty, or more years being not uncommon.

The actual death rate is impossible to fix, on account of the great variation in the severity of the symptoms, the fact that a relatively large proportion of severe cases is reported, and that death is often due only indirectly to the disease itself, often to complications or accidentally associated diseases. Buschan's figure, 11.6 per cent., is of limited value only, and a better index of the danger than higher figures in chronic cases. Hospital statistics, showing a death rate of 30 per cent. in acute cases, do not apply to the majority of cases found in general practice.

Among the causes of death cardiac weakness is most important. Next comes exhaustion from vomiting and diarrhœa, fever, and other toxic phenomena. Pneumonia and tuberculosis are common terminal diseases. Death after operation is usually due to cardiac failure.

Treatment.—The number and variety of modes of treatment for exophthalmic goitre, and the confidence with which the most diverse methods are lauded prove that something more is effective in favorable cases than medication. The essential things we may believe are the frequent tendency of the disease to improve, the general measures that are carried out with the other details, the expectation of help on the part of the patient, assisted by the relief of various symptoms, either from general or special treatment. In the absence of a causal treatment it is proper to begin with the empirical method.

The muscular weakness, the condition of the heart, and the nervous irritability, as well as the increased metabolism in exophthalmic goitre, all indicate the necessity of rest. This must be adapted to the patient. In severe cases or stages the most rigid details of the rest cure are necessary. These need not be described here, but the application of rest in milder cases requires further consideration. General statements to patients are useless; it may be impossible to secure rest in bed at fixed hours, and in many cases the rest can be obtained better in other ways. Long hours of sleep are beneficial, and the patient should retire as soon as the work of the day is over. Late hours should be avoided as much as possible, but when they appear necessary should be preceded and followed by rest of sufficient length. In the daytime the patient should lie down rather than sit, and sit rather than stand, but there is usually no advantage in sleeping in the daytime, and if done it often prevents sound sleep at night. It is possible for patients to take even several hours of rest daily on a couch, cot, or even the floor, convenient to the usual working place, when going to bed would either be impossible or would

involve more work than could be made up by the rest following. So far as possible stair-climbing should be avoided.

Exercise should not be permitted in the beginning of treatment. Massage and passive exercise may take its place for a time. After the necessary improvement has been obtained gradually increased exercise should be encouraged. Patients must always be plainly instructed regarding exercise, and its amount should be based upon the necessary work done by the patient. Both work and exercise should stop short of fatigue on the whole, and at any time of the day.

Mental rest is just as important as physical rest. It can be secured in patients who do not need rigid seclusion by avoiding all unnecessary or harmful activity. Necessary or congenial occupations can usually be carried on, cheerful company should not be shunned, but all exciting and depressing occupations should be given up. Reading, sewing, and all diversions and amusements need to be investigated by the therapeutist with reference to the individual. Dancing is often injurious. Exhausting tours are dangerous, but leisurely travel is often good for patients without severe symptoms.

Hydrotherapy has been used with benefit. In most cases it is enough to see that bathing is done to the necessary extent, and to prevent exhausting and depressing baths. As regards clothing, tight collars and excessive lacing should be avoided.

The *diet* should be as varied as possible, and in amount such as to increase the weight if not to bring it to normal. The scales should be used regularly as a guide to progress. All anomalies on the part of the stomach must be corrected. Overfeeding must be carefully avoided. Frequent smaller meals are usually preferable to few large ones. It is not necessary to exclude meat. Milk, buttermilk, and fermented milk are all useful, but coffee and tea must not be taken in excessive quantities. All indigestible and stimulating foods and condiments should be avoided. Alcohol should not be used if it causes symptoms, and is not necessary in any case.

The patient should get as much fresh air as possible, and as this cannot be taken in sufficient amount in the usual way, by walking or driving, the patient should spend as much time as possible reclining out of doors, well protected from cold and wind. The bed room should be well aired, or the patient may with advantage sleep out of doors. In the latter case it is essential that sleep be not lost by early waking from light that can be excluded. Climatic treatment is rarely necessary. If patients desire a change, moderate elevation, pure cool air, and freedom from high winds should be sought. The seashore is usually not favorable, and high elevations are also often unfavorable for the heart and the nervous symptoms. The physical and mental occupations must be carefully ordered at climatic resorts.

The general measures are beneficial to many symptoms, but other details are often necessary. Tachycardia and palpitation usually subside quickly under rest, although they may have resisted all medicinal treatment. In general, no drug should be given for the heart in the beginning of treatment unless rest is secured. If rest alone does not quickly reduce the pulse rate, a light ice-bag should be put over the heart, constantly or intermittently, according to the effect. If there is much vascular excitement in the thyroid or the cervical vessels, an ice-bag or coil may be applied there.

Of cardiac stimulants, digitalis should only be used when there is cardiac weakness, and even then must be carefully watched. Arhythmia and

gastric irritation may be caused by it. If necessary to give it, it should be omitted every other day, or every third or fourth day, according to the conditions. In mild cases strophanthus (the tincture, 5 to 10 minims) gives good results and is much more easily borne than digitalis. Strychnine also is useful in these cases. Belladonna or atropine is thought by some to lessen the overactivity of the thyroid. They have also been used to lessen the excessive sweating, but other measures are more useful.

For nervousness, restlessness, and insomnia, rest, fresh air, a cool bedroom, and comfortable bed are more important than drugs. A neutral bath (95° to 96°) of fifteen to twenty minutes may be given before retiring. Sometimes a hot drink, or a hot water bag to the feet, possibly also one to the epigastrium, proves beneficial. If restlessness resists these measures, a full dose of bromide should be given at bedtime, one dram of the sodium salt, repeated in an hour if necessary. This is much better than a smaller dose repeated night after night. Pure hypnotics are rarely necessary. Opiates should never be used in cases that have any chance of survival. The severe psychical disturbances, mania and delirium, require treatment as under other conditions. Asylum treatment is rarely necessary.

For the stomach and intestines, regulation of diet suffices in many cases. Strychnine is sometimes useful as a stomachic, or small doses of quinine may be given before meals. Constipation should be avoided by diet, water, and regular habits as far as possible. As a further aid, a mild laxative, such as cascara sagrada or sodium phosphate, should be used in appropriate doses. Sodium phosphate has been considered a sort of specific by many besides Trachewsky and Kocher, but the writer has never seen evidences of that, even when given in doses of 20 to 80 grains from one to three times a day. Many use mercurials at short intervals. With care and milder measures they are unnecessary.

In gastric and intestinal crises, the stomach and bowels should be evacuated by lavage, cathartics, and enemas. Simple diet, such as gruel and albumin water, should be used for a few days. Bismuth and antiseptics, such as salol, often seem beneficial, but opiates and astringents should be avoided as much as possible. The anæmia rarely requires iron or arsenic. They have no specific action upon the disease, but may be used for positive indications on the part of the blood. Pallor is by no means evidence of anæmia in patients with exophthalmic goitre, nor is flushed skin a sign of plethora.

Fever, if present as a complication or in severe cases, should be treated by tepid sponging, tepid full baths, or cold full baths, according to the indications.

Irritation and ulceration of the cornea or conjunctiva, from exposure, should be treated with boric acid solutions in the beginning. Special treatment should be applied if the treatment is not quickly beneficial. Tarsorrhaphy, for cosmetic or protective purposes, has never made itself a place. Fortunately the most severe exophthalmos is rare.

Other complications should be treated according to the special rules for such conditions.

Iodine and iodides have been used a great deal in the treatment of exophthalmic goitre, and often reduce the size of the thyroid. Some patients improve generally under or after the treatment. On the other hand, others are made worse, having palpitation, headache, nervousness, etc. It is obvious that the diminution in the size of the gland under iodine does not indicate, necessarily, a reduction of the process that causes the hyperthyroidism. If

no bad effects are produced, it may be useful to affect the simple goitre by careful iodine treatment, but it should always be remembered in this disease that iodine may be the "drop that makes the vessel run over." Breuer even warns against iodoform on dressings over thyroid wounds. The use of ointment of red iodide of mercury, once relied upon to reduce the size of the gland, is now almost wholly abandoned. Injections of iodine, iodoform, and the like to reduce the gland are more dangerous than surgical operations.

Electricity has been much used, and excellent results have been reported. It may be admitted that under the use of weak currents many symptoms subside, but it is instructive to see that while one operator uses a certain kind of current, as the galvanic, others insist that only the faradic current is useful, still others static, high frequency, or some other variety. It seems that the chief benefit is rather due to the associated general measures, or to suggestion from belief in a potent and mysterious means of cure.

Suggestion doubtless plays an important part in all successful methods of treatment of such a disease, and should be utilized in a rational manner, but hypnotic suggestion is unwarranted.

Röntgen rays have been used with varying results. C. H. Mayo thinks they lessen vascularity, induce sclerosis around the gland, and so diminish the risk of hemorrhage at operations. R. Freund[1] has recently reported some favorable results, with a review of the literature. F. R. Cook[2] relates the most far reaching effects. The writer has treated several cases, and, although local and general improvement sometimes followed, was not convinced that the treatment was of real value. The use of radium in the gland, as practised by Abbé, does not seem to have been distinctly beneficial, and is not likely to be widely imitated.

Organotherapy.—Very soon after the rise of modern organotherapy, thyroids, fresh and dried, and also iodothyrin, were used in exophthalmic goitre. With various preparations the goitre often becomes smaller, and in some cases other symptoms also improve, but in others they grow worse. According to the hyperthyroidism theory, the latter seems inevitable, unless the preparation is inert. There are some, however, who believe the matter not so simple. If altered secretion is the cause of the disease, the ingestion of a normal gland substance or its active principle may be capable of assisting the function of the gland until it becomes improved. Mackenzie also suggests that thyroid treatment may be useful in old cases with deficient secretion. On account of the lack of accurate knowledge of the strength of thyroid preparations and the danger of producing alarming symptoms, they do not seem at present advisable.

From the frequent finding of an enlarged thymus in exophthalmic goitre, and the idea that it might be compensatory, thymus preparations have been used by Mikulicz, S. Solis Cohen, O. T. Osborne and many others. Even before planned experiments, Owen, through the mistake of a butcher, fed a patient on thymus, and only discovered the error after the case had been reported as one of improvement under thyroid feeding. Thymus has also been supposed to act by its iodine content, but this does not recommend it. A number of patients have taken it without benefit, and more experimental work should be done before it is prescribed.

[1] *Münch. med. Woch.*, 1907, No. 7.
[2] *Journal of the American Medical Association*, 1908, I, 758.

A wholly different method was originated by Ballet and Enriquez (1895), who tried to neutralize the poison of the Basedow thyroid by giving the serum of thyroidectomized dogs. Similar experiments were made with the milk of thyroidectomized goats (Lanz) and sheep, the blood of a myxœdema patient (Burghart), the thyroid of a cretin (Moebius). At present the available remedies of this class are: Antithyroidin Moebius (dose 8 to 60 gtt., 0.5 to 4 cc., t. i. d.), prepared from the serum of thyroidectomized sheep and preserved by the addition of 0.5 per cent. carbolic acid; rodagen (75 to 150 grains, 5 to 10 grams a day), prepared from the milk of thyroidectomized goats and triturated with milk sugar; and thyroidectin (dose 5 to 50 grains t. i. d.), made from the blood of thyroidectomized sheep. The fresh milk of thyroidectomized goats, from six weeks after operation, has also been used, but many patients acquire a disgust for it. The milk of one goat, up to three pints a day, may all be taken by the patient.

Under treatment with all these preparations the changes observed are about the same. The enlarged thyroid becomes smaller and softer. Of the other symptoms, the most distinct effect is seen on the heart, as in all other methods of treatment. Irritability and weakness are sometimes improved, but very often they are not. A few patients quickly begin to improve, but in the majority the progress is slow. The dosage is of course a matter of guesswork. We do not know how much toxin we have to neutralize, nor how much antidote there is in a given amount of the remedy. The customary method is to increase the dosage as rapidly as possible, beginning with the minimum, and adding as much every day until there is a marked improvement or signs of intolerance, and then to decrease, continue, or stop altogether, according to the condition. Rodagen and antithyroidin sometimes become objectionable, the former from its peculiar odor, the latter from its phenol. Thyroidectin is less disagreeable. It, and probably the others, seem to form a habit, so that even patients who are not greatly benefited by it find it difficult to abandon the drug. All the preparations are expensive.[1]

A different method was adopted by Murray,[2] and by Beebe and Rogers.[3] The latter, who have carried out a large series of experiments, obtained a serum by injecting the nucleoproteid and the thyroglobulin from thyroids of Basedow patients (obtained at autopsy) into rabbits. Later, thyroids removed at operations were used. Besides the "pathological" serum, a "normal," "antitoxic," or thyroidal cytotoxic serum was obtained by using the nucleoproteid and thyroglobulin of normal human thyroids. It is too early to speak of the effects of this class of preparations; Rogers and Beebe take a very cautious and conservative standpoint. The preparation of the serum is attended with obvious difficulties, and those who wish to repeat the observations should have a sound experimental basis.[4]

Surgical Treatment.—In the last few years the results of the surgical treatment of exophthalmic goitre have forced the importance of such measures upon our attention. At first glance it seems reasonable that if there is hyperfunction, removal of the redundant tissue or its reduction in size would cure

[1] Bulkeley, *Boston Medical and Surgical Journal*, 1907, clvii, 626.

[2] *The Lancet*, 1905, ii.

[3] *Journal of the American Medical Association*, February 17, 1906, pp. 484, 487; *Transactions of the Association of American Physicians*, 1906, pp. 513, 549, 577 (discussion); *Archives of Inter. Medicine*, 1908, p. 297.

[4] See also Ewing, *New York Medical Journal*, 1906, lxxxiv, 1061.

the disease. When, however, we remember that we cannot remove the whole of the thyroid gland, that we cannot tell, when we take out a part, whether the remaining portion is not relatively more dangerous, and when we recall how hypertrophied tissue may keep on growing or grow more rapidly if partially removed, it becomes clear that the theoretical basis of the treatment is very incomplete.

Since Rehn first operated, in 1884, so many cases have been reported that we can deal with facts. As an example of the statistical evidence, we find that Kocher[1] has had 254 patients, with 315 operations, up to 1907. Mayo has had about as many; Halstead reported, up to June, 1907, some 90 cases. These few figures are as convincing as much larger tables that could be compiled from the reports of many other operators. The operations include all kinds of cases, recent ones as well as those of long-standing, severe ones and mild ones. The general result is very good. After the first few days immediately following operation there is usually a marked improvement, first seen in the tachycardia and other heart symptoms, soon after in the tremor and other nervous symptoms. Even the exophthalmos sometimes disappears, although in cases of long duration it cannot be expected.

As to the thyroid, the part left in does not always hypertrophy. Many operators, including Kocher, Reverdin, Poncet, Woelfler, and C. H. Mayo, say that it contracts. In some cases, however, hypertrophy occurs, with return of the symptoms, and sometimes requires a second operation.

Recovery, of course, does not always occur. Death ensues in a proportion varying partly according to the condition of the patients treated, but chiefly with the skill and experience of the operator. Kocher had 9 deaths out of 254 patients, 3.5 per cent., and none in the last 63 of the series, with 91 operations. Mayo lost 4 out of the first 16 cases, but only one in the last 75. Although all operators lost many patients in the early part of their work, this was not due so much to lack of technical skill as to making too extensive operations. The modern operations, although dangerous, are much safer than the early ones.

As regards the selection of cases, an important factor bearing on the completeness of the recovery is the condition of the patient. Cachectic patients, with advanced heart weakness and extreme exophthalmos, should not be urged to undergo operation, although even they may be helped. It is better to operate early in patients not distinctly improved by thorough treatment with rest and other measures, or in those who are not able to take such treatment, at as early a time as possible. Special indications are severe symptoms, especially toxic symptoms like tachycardia, and loss of strength. Local signs, as of pressure, or suspected adenomatous change, also indicate operation.

The operations most practised now are partial resection, or ligation of two or three of the thyroid arteries. Crushing, ligating en masse, exothyropexy, or open resection have no advantages, and are not practised by the operators of greatest experience. Sympathectomy has sometimes given good results, but also many failures, not always reported, and is now abandoned by operators of experience. The chief danger in thyroid operations is from heart failure. This is to be prevented, so far as possible, by getting the patient

[1] *Journal of the American Medical Association*, October 12, 1907, p. 1240 (with discussion).

in the best possible condition by rest, the ice-bag, and cardiac tonics. C. H. Mayo does not operate if the pulse is above 130, or varying in force and frequency, or if there is anæmia or œdema. In such cases he has treatment with *x*-rays and belladonna carried out. According to Kocher, high blood pressure is not a contra-indication, but cases with low pressure need careful treatment before and after operation.

Symptoms of hyperthyroidism, tachycardia, bounding pulse, sleeplessness, nervousness, vomiting, and diarrhœa sometimes occur in the few days following the operation. This sequence has been explained in various ways, especially by the absorption of thyroid secretion. It varies in frequency in different clinics. Kurt Schultze denies intoxication by thyroid juice. Mayo also says it is not due to forcing secretions into the wound by rough handling. It comes on too late for that, and hence must be due to absorption from the gland. McCosh never saw bad results from handling the goitre, but saw a case, fatal within twenty-four hours, in which the superior thyroid arteries were ligated, without manipulation of the thyroid gland. Capelle's[1] observations point to the relation of the enlarged thymus in these cases and emphasize the need of clinical and other study of that gland in Basedow's disease. Loss of blood favors it. Mayo points out that in these patients other operations may bring out hyperthyroidism. Adrenalin, atropine, and morphine can be used in the treatment of the condition. Kocher, who ascribes the symptoms to hemorrhage and absorption of toxic blood, says it can be almost entirely avoided by care in technical details.

The danger of tetany is now largely avoided by care in the operation. The same is true of injury of the recurrent nerve.

The object of resection is to remove all excessive tissue, leaving about 30 to 60 grams. In some cases too much is taken, myxœdema symptoms follow, and require treatment with thyroid preparations, or grafting.

As the operation is one that should only be performed by surgeons of experience and knowledge of the special features, it is not necessary to describe the technique. Certain details are matters of choice. Kocher recommends local anæsthesia; Mayo, general anæsthesia with ether. In exophthalmic goitre the thyroid is rarely large enough to make general anæsthesia especially dangerous, and on account of shock a general anæsthetic seems desirable. Coughing is an undesirable sequel, but occurs sometimes even with local anæsthesia. Vomiting and secondary hemorrhage are particularly dangerous, and the latter is to be avoided by the most careful ligation of vessels and observation of the wound afterward. Kocher and Mayo recommend ligation of the superior thyroid arteries in mild cases, or in severe ones as a preliminary. Ligation is not without dangers.

After an operation for exophthalmic goitre the general and hygienic treatment should be continued until the patient is as well as possible, and later the occurrence of symptoms should lead to a careful examination, in order to discover and treat a relapse as promptly as possible.

[1] *Beiträge z. klin. Chir.*, 1908, lviii, 353; *Münch. med. Woch.*, September 1, 1908.

CHAPTER XVIII.

ATHYROSIS. ATHYREA. ATHYROIDISM. HYPOTHYROIDISM. CRETINISM. MYXŒDEMA.

By GEORGE DOCK, M.D.

The development of our knowledge of diseases due to loss of thyroid function has already been described. It is not necessary here to do more than remind the reader of the observations and reports of Gull and Ord, the recognition of the resemblance of cachexia strumipriva to myxœdema (Reverdin and Kocher), the experimental work of Schiff, Semon, Horsley, and others in the latter part of the last century. The implantation experiments of von Eiselsberg and Serrano and Bettencourt were soon replaced in treatment by the hypodermic method of Murray and the less troublesome and equally efficient internal administration, demonstrated by Howitz, E. L. Fox, and H. Mackenzie. By this time, only about fifteen years after Sir William Gull's publication, the clinical features of myxœdema had become thoroughly known and the pathology and treatment put on a basis not equalled by many diseases.

The coincidence of goitre and cretinism had been known since the time of Paracelsus (1616). From the end of the eighteenth century, and especially in the middle of the nineteenth, there was wider attention to the subject on the part of philanthropists and statesmen, but accurate study was not at first correspondingly increased, and under the term "cretinism" an inextricably confused series of cases—true cretins, rachitic dwarfs and idiots of all kinds—was thrown together. Sporadic cretinism was recognized early (Curling, 1850, Fagge, 1871), but it was not until myxœdema was fairly well known that the relation of all three forms could be accurately considered. The observations and animal experiments of Halsted, Hofmeister, von Eiselsberg, and Lanz cleared up many of the obscurities.

It is now accepted that goitrous degeneration is only one of many causes of loss of thyroid function. (Goitre, of course, does not always produce such conditions as we are about to describe.) Besides operative removal of a large part, functionally speaking, of the gland, various chronic atrophies, acute inflammation, and unknown factors play their parts. The effects upon the individual vary chiefly according to the age at which they operate. The earlier it occurs, the more the condition that results resembles cretinism; the later, myxœdema. Until recently tetany was included among hypothyroid or athyroid conditions, but it is now certain that the former has only accidental relations with loss of thyroid function.

The known results of hypothyroidism or athyroidism are:

1. Congenital myxœdema (congenital cretinism).
2. Infantile myxœdema (endemic and sporadic cretinism).
3. Spontaneous myxœdema of adults.

4. Postoperative myxœdema.
   (*a*) From total extirpation of the thyroid.
   (*b*) From almost complete extirpation.
   (*c*) From atrophy of the gland after operation.

Many other conditions, especially certain forms of infantilism and obesity, are classed by some writers as hypothyroid states, but their position is not yet sufficiently settled to permit classifying them with those mentioned above.

CRETINISM.

Endemic Cretinism.—Synonyms.—Endemic cretinism; cretinoid idiocy; cretinismus (Latin); Kretinismus, endemischer Kretinismus (German); crétinisme (French); cretinismo (Italian and Spanish).

The word cretin is usually derived either from (French) Chrétien, "innocent," or creta, "chalk;" the former referring to a widespread idea, the latter to the color of the skin. A more reasonable derivation is suggested by Bayon,[1] viz., from Rhaeto-Romanic cret, "cripple," "dwarf," cretin, "diminutive." As the same author remarks, athyrosis or hypothyrosis congenita or endemica would be preferable, since the term cretin is historically too general.

Etiology.—The etiology of endemic cretinism is as obscure as that of endemic goitre, with which it has such close geographical relations. The disease occurs in some but not all foci of endemic goitre. It is very common in the severe goitre districts of Europe, rare in many milder areas, like those of North America and England. All statistics in regard to the frequency of cretinism contain an error from diagnostic mistakes. The figures given under goitre, and the proportion stated for Carinthia and Salzburg (district), 293 and 276 per 100,000 population respectively, show the importance of the disease economically. When people migrate into such a district, goitre is likely to show itself in the first generation, cretinism in the later ones. Females are more often affected in the proportion of 2 to 1. In goitre regions, cretins have goitrous mothers, or one or both parents are mild cretins. In some cases it seems as if congenital cretinism were derived from the mother, that occurring later, from the father. Not all goitrous parents beget cretinous children. In cretinous lands, marriage of two cretins is either sterile, or the infants are not viable.

Pathology.—Notwithstanding the close relations between goitre and cretinism, the exact pathology of cretinism is not yet agreed upon. Bircher especially opposes the view of identity of cause. Buschan considers cretinism a mixture of myxœdematous cachexia and degeneration. Since removal of a goitrous thyroid from a cretin may be followed by myxœdema, cretinism may be looked upon as an incomplete myxœdema.

The most striking anatomical feature of endemic cretinism is the abnormal skeleton. This is characterized by an arrested or retarded development of the bones, and not, as long believed, by early ossification. The retardation is due rather to a general disturbance of nutrition than to a specific interference with any of the processes of bone formation. The character of the bony change depends upon the period of growth at which the disease

[1] *Beiträge zur Diagnose und Lehre von Cretinismus*, etc., Würzburg, 1903.

begins. The earlier the thyroid change, the more marked the alterations of the bones. Bone development in cretins sometimes continues beyond the usual period, as shown by Wagner.

The skull is remarkable for its low forehead, deep and broad root of the nose, prominent malars, and prognathism. It may be large or small, broad or narrow. The spheno-occipital fissure is not closed prematurely, but has been found open at fourteen months (Langhans), twenty-four years (Klebs and Langhans), or cartilaginous at fifty-eight years (His). The bones of the extremities, and also the ribs, are short and thick, sometimes deformed. They may seem to resemble rickety bones, but they show no proliferation in the zone of development of the epiphyseal cartilages, and, on the other hand, exhibit delayed ossification (Langhans, Hanau, Bircher, Hofmeister, von Wyss, and others). In some cretins examined at advanced age (fifty to sixty years) ossification has been complete, but there is no rule. The pelvis is narrow. P. Müller, who finds narrow pelves especially frequent in Bern, ascribes them to cretinism. Histologically, cretinous bones are characterized only by the lack of ossification. Periosteal changes are not constant or peculiar.

Thyroid.—In the majority of cases of cretinism there are goitres of various kinds. Sometimes in the most severe cases the thyroid gland is absent (10 per cent., Wagner), sometimes small or normal, but never the latter with a normal structure. The microscopic structure of the cretinous thyroid has been worked out by Hanau and de Coulon. It shows an extreme atrophy of the epithelium, with thickening of the colloid. The thymus is often persistent.

Clinical Features.—Cretins are of low stature, usually from 1 to 1.5 metres (forty to sixty inches) in height when full grown, sometimes less, 89 cm. at twenty-two years, 91 cm. at thirty-seven years (Wagner). They are not smaller than other infants at birth. The body is short and broad, and that, with the low, broad forehead, flat nose with conspicuous nostrils, small eyes widely separated, the stolid expression, and muddy skin, suggests the Esquimo, but in the more severe cases the thick and blubbering lips, open mouth with large protruding tongue, add a semibestial aspect repulsive in the extreme.

The neck is short and thick; the thorax short, hollow, and in the female lacking in mammary development. The abdomen is large and pendulous. The legs are short, sometimes crooked, with small and weak muscles. The skin has characteristic changes; it is of chalky pallor, sometimes varied by brownish pigment, and is thick, inelastic, and cold; it looks œdematous, but does not pit on pressure. This myxœdematous condition sometimes disappears in the course of the disease. On the forehead the skin is wrinkled, and on the buttocks and genitals it is often in folds. The supraclavicular fossæ contain cushions, as in myxœdema; the submucosa of the mouth and pharynx is also sometimes thickened. The skin is usually dry and scaly. Sweating is scanty or absent. The hair is thin, coarse, and dry; scanty on the body; the beard does not grow. The nails are brittle, the teeth carious. The genitals remain undeveloped, as a rule, sometimes develop between the thirtieth and fiftieth years, but rarely to a stage making procreation possible. The body temperature is low, the gait weak, waddling, or uncertain, sometimes limited to creeping.

Idiocy is an essential part of cretinism. It is parallel to the lack of

development of the skeleton and genitals, assisted by deafness and anomalies of other special senses. In some cases deafness may be due to adenoid swellings in the pharynx. It, with lack of training, makes it difficult to test the degree of intelligence or lack of intelligence of a cretin. Sometimes only a few inarticulate sounds can be elicited. Individuals with less complete bodily and mental change are spoken of as "semicretins." Cretins are always apathetic, stupid, and lacking in memory and decision. They are not easily excited, but are sometimes vindictive. They can sometimes be trained to simple duties and become "hewers of wood and drawers of water." These, sometimes spoken of as "beast men," have about the mental development of a trained house dog (Kocher); others, less developed, are spoken of as "plant men." The vegetative functions are often good. The cretin is usually a great eater, but careless; he swallows food without chewing and easily overloads the stomach. The subjects of endemic cretinism sometimes reach fairly advanced age, fifty or sixty years.

Treatment.—The prophylaxis of endemic cretinism is a serious economic and social problem, like that of endemic goitre. Improvement of hygienic conditions and pure drinking water are essential factors. The treatment of individual cases may be carried out on the same lines as those given for sporadic cretinism. The improvement will depend chiefly upon the age, but even at ages when growth has in general ceased some improvement is possible. Growth and nutrition, including that of the skin, and also the intelligence, improve under thyroid medication, which must be kept up for years, probably for life. Wagner has seen good results from iodine treatment, and besides giving cretinous persons the benefit of sea air, as has long been proposed, it has been suggested that they be given iodine in minute doses, possibly in table salt, as Kocher recommends.

Sporadic Cretinism.—**Synonyms.**—Sporadic cretinism; congenital or infantile myxœdema; idiotie avec cachexie pachydermique; pachydermie crétinoide; idiotie crétinoide (French); infantile Myxidiotie (German).

Definition.—Sporadic cretinism is a disease nearly related to endemic cretinism and to myxœdema, but occurs where cretinism is not endemic, is characterized by imperfect development of the body and intellect, and is due to lack of thyroid secretion.

Etiology.—Thyroiditis from or in an infectious disease—such as measles, enteritis, or typhoid fever—or trauma, is probably one of the most important causes of sporadic cretinism. Tuberculosis, bad hygienic surroundings, alcoholism, and emotional shocks in the parents, especially at the time of procreation, or in pregnancy, are often mentioned in case histories. Infantile myxœdema sometimes occurs in two or more children of the same parents. Thyroid anomalies are not always possible to recognize. Paterson[1] reported a family in which two cases of myxœdema occurred. In the third pregnancy the mother took thyroids from the fourth month, and a normal child was born. MacIlwaine has reported the cases of mother and child.[2]

Pathology.—The pathological anatomy is essentially like that of endemic cretinism. The undeveloped bones can easily be demonstrated during life by skiagraphy and the stage of ossification determined. The thyroid is sometimes goitrous (7 out of 60 of Osler's cases[3]). In most cases it is

[1] *Lancet*, 1897, ii, 849. [2] *British Medical Journal*, 1902, i, 1261.

[3] "Sporadic Cretinism in America," *Transactions of the Congress of American Physicians and Surgeons*, 1897, p. 169.

PLATE II

FIG. 1



FIG. 2



Sporadic Cretinism, aged 21 years. (Case of Dr. Hermon Sanderson.[1])

Fig. 1. Before treatment.

Fig. 2. After four months' treatment.

FIG. 3



FIG. 4



Sporadic Cretinism.

Fig. 3. Four years old, beginning of thyroid treatment.

Fig. 4. Five years old, thyroid treatment for one year.

[1] Sporadic Cretinism, with Report of Three Cases in One Family. *Michigan State Medical Journal*, April, 1906.

atrophied, as Fagge pointed out. Usually there is widespread atrophy, with very few acini preserved. In some cases there are microscopic evidences of hyperplasia. In a case mentioned by Adami, with myxœdematous changes of the hands and some other parts, and with cancer of the pituitary, there was no change in the thyroid. In many cases the thyroid is so small that it is supposed to be absent, or is found only after careful search in serial sections, as in the case of a myxœdematous idiot reported by MacCallum and Fabyan.[1] The skin shows changes like those in myxœdema. MacCallum and Fabyan describe a peculiar condition of the fat in the subcutaneous tissue, occurring in fine droplets in the fat cells, instead of one large drop.

The condition of the thymus requires investigation. In some cases the hypophysis has been found enlarged. The brain is small, and the ventricles contain an excess of fluid.

Symptoms.—The disease is frequently congenital, but the symptoms rarely show themselves, at least well enough to make recognition easy, until the second year. This is usually attributed to the protective action of the mother's thyroid secretion in the milk, or to milk diet. After weaning, both these influences are lost. There is little or no bone growth, so that the infant bids fair to become a dwarf. The fontanelles remain open, but evidences of rickets are usually absent. The teeth do not appear, or do so very late, and are imperfect. The muscles are small and weak, the abdomen large and pendulous, with umbilical hernia, as a rule. The skin and mucous membranes are thick, the former either from fat or from the myxœdematous infiltration. The hair is coarse and grows poorly. There is anæmia with leukopenia.

The thyroid is usually atrophied. The bony skeleton acquires the cretinous characteristics. In the early months nothing abnormal can be recognized in the skiagram. Later the absence of ossification of the epiphyses, especially in the phalanges, is evident. Mental and physical development both seem at a standstill. The infant does not smile at the usual age, nor does it begin to walk. The figure becomes more and more cretinoid.

Infantile myxœdema varies in its features according to the stage of development at which the loss of thyroid function makes itself felt. If it occurs after the first year the fontanelles are closed. The length of the body and the degree of ossification are in proportion to the age at which the disease began. In such cases previous rickets may have affected the bones so that the changes are not merely those of arrested ossification. Besides the stunted growth, the parts of the body do not show normal proportions. The head is relatively large, the face broad, "full moon;" the eyes wide apart, the lids thick; the ears are large, of waxy appearance; the root of the nose is low, the nostrils broad and flattened ("bull-dog" or "pug" nose). The lips are thick, protruding, and usually open and cyanosed; the tongue large. The chin is short, but there is often a "double chin," below the jaws, on the short, thick neck. The teeth are often carious or imperfect, but the former varies much with the care of the mouth, the latter with the age at which the disease comes on. Salivation is usual. The head drops forward, the upper vertebræ are curved, with the convexity backward, the lumbar spine often having an opposite curve, increasing the protuberance of the abdomen. The

[1] *Johns Hopkins Hospital Bulletin*, September, 1907, xviii, 341.

abdomen has the "frog-belly" shape, and usually shows an umbilical hernia or pseudohernia, containing fat but no intestines. The pelvis is small. The penis and scrotum are usually small, the clitoris and labia often œdematous. The legs are short. The tibiæ are sometimes curved, even without rickets or in the absence of thyroid treatment. The epiphyses may be enlarged. The hands are clumsy, "spade-like," or resemble paws. The extremities are usually cyanotic. The skin is thick, leathery, or tough, yellow, wrinkled, and dry. Perspiration is usually but not invariably absent. The hair is sparse, coarse, and dry. The thyroid is usually impossible to feel, but may be present, even goitrous. There may be soft, fluctuating masses of fat above the clavicles, in the jugular fossæ or the axillæ, not always symmetrical. The temperature is subnormal; there is great susceptibility to cold. The blood shows distinct anæmia, sometimes as low in hæmoglobin as 50 to 60 per cent.; the red cells vary in size and shape; the leukocytes are not increased. The mental condition varies, according to the age and development at onset, from mild to severe idiocy. Myxœdema in childhood without idiocy has been described by Marfan and Guinon, Brissaud, and others. In most cases the idiocy is of moderate degree. Deafness, from adenoids or from middle ear disease, is very common, and has an important part in the failure of mental development. The patient can learn easy sentences, can be trained to some extent, but is dull, or apathetic or stupid; slow and awkward of gait, and difficult or impossible to arouse to mental or physical exertion. Anger and severe depression sometimes occur. Some patients are vicious, almost all dirty, and more or less helpless. Chvostek's phenomenon is usually present. The appetite is usually good, but there is often a repugnance to meat. Constipation is the rule.

Varieties.—It is possible to subdivide cases of sporadic cretinism according to the stage of growth at which the loss of thyroid function became affective, both bodily and mental symptoms showing fairly constant relations, but the intermediate stages are so numerous that such a classification is only of general application.

We can distinguish, with Combé:[1] Congenital myxœdema, with complete arrest of physical (dwarfism, "nanism") and mental (idiocy) development; early infantile myxœdema, occurring in the first year, with less marked dwarfing and some intelligence, amounting to imbecility or semi-idiocy; late infantile myxœdema, occurring in the second or third year, with small body and inferior intellect. To these can be added the incomplete (fruste) form of atrophic myxœdema, corresponding, for the age of the patient, with mild myxœdema of adults.

Diagnosis.—If the disease is known to the physician by experience, mistakes can hardly occur with fairly typical cases, or with atypical ones if the course can be followed for a short time. Knowledge based only upon reading, with a study of portraits, should enable one to recognize the disease without great difficulty, but has often led to erroneous diagnoses. A thorough examination of the patient is essential, and in most cases a careful differential diagnosis is necessary to prevent error. Patients with severe infantile dystrophies have a strong resemblance in certain ways, and a hasty conclusion, based on the facies for example, should be avoided, much more one

[1] *Traité des maladies de l'enfance.* By Grancher, Comby, and Marfan, 1897.

based on idiocy. It is useful to consider the chief causes of error, and to learn the differential diagnostic features in each case.

The possible causes of error are rickets, dwarfism, Mongolian idiocy, achondroplasia, congenital adiposity, diffuse scleroderma of the newborn, and hydrocephalus. In all of the four first mentioned there is lack of growth, most marked in myxœdema and achondroplasia, and especially abnormality of bone growth. Rickets is frequently assumed when myxœdema is present, on account of deformities of the bones.[1] In all stages the differences between the swollen epiphyses and irregular epiphyseal boundaries of rickets and the lack of ossification of myxœdema are easy to demonstrate by skiagrams. Dwarfism ("nanosomia" is etymologically less accurate than "microsomia"), or microsomia, includes two classes, the pure dwarfs (microsomia simplex), miniature but well-formed people, and the much less rare microsomia infantilis, or infantile dwarfs, sometimes called "type Lorain," following congenital or acquired disease. The combination of idiocy and infantile dwarfism is difficult to distinguish from myxœdema, but can be recognized by the absence of the characteristic skin changes and of the cretinoid facies, the occurrence of sweating and the difference in the bones. Ateleiosis of H. Gilford[2] cannot be mistaken for sporadic cretinism.

Mongolian idiocy is not admitted by many observers as an independent disease. Many English writers consider it sporadic cretinism; Bayon thinks its existence unproved. It requires confirmation, and the name should only be applied to congenital idiots in whom there is a Mongolian slant of the eyes, with epicanthus. In many cases reported there was restlessness instead of the apathy of the cretin. Although myxœdema patients may have epicanthus, the other features of the facies of the latter are absent in Mongolian idiocy. Achondroplasia (micromelia, fetal chondrodystrophy) may be mistaken for cretinism, as in the classic experience of Virchow. Its most striking feature is the shortening of the extremities, much more marked than occurs in sporadic cretinism and absent in rickets and Mongolian idiocy. The cold skin and low temperature of the cretinoid, often with a slow pulse, is an important feature in distinguishing sporadic cretinism from the other diseases. The spade-like or paw-like hands of the latter usually differ plainly from the beaded hand of rickets and the "trident" hand of achondroplasia. In all suspected cases the size and condition of the thyroid gland should be investigated. Practice in all kinds of subjects will make this part of the examination more certain. In doubtful cases a careful trial with a thyroid preparation should be made. Slight improvement may occur under the use of thyroid in some of the other conditions, but nothing like the specific changes in myxœdema. Congenital adiposity may be of thyroid origin. It can be distinguished from more marked hypothyrosis by careful attention to the symptoms. The same may be said of diffuse scleroderma neonatorum. Myxœdematous subjects may have hydrocephalus, but the ordinary subject, with high, overhanging forehead, can readily be distinguished from the cretinoid by a full examination.[3]

[1] The ingenious claims of Hertoghe (*Die Rolle der Schilddrüse bei Stillstand . . . des Wachstums*, translated by Spiegelberg, Munich, 1900) for the identity of rickets and hypothyrosis are not admitted by other students of both diseases.

[2] *British Medical Journal*, 1904, ii, 914.

[3] Useful differential diagnostic points with skiagrams are given by Siegert (*Jahrbuch für Kinderheilkunde*, Band liii, p. 447) and by Hermann (*Archives of Pediatrics*, 1905, xxii, 493).

Prognosis.—Infantile myxœdema, if not treated, has a slow but sure course. The older the patient grows, the more marked are the symptoms. Improvement does not occur, even temporarily. The duration of life is short, usually less than thirty years, although some patients live to thirty-five, forty, or even fifty. Death is usually due to intercurrent disease. The modification in course and prognosis under specific treatment will be described later.

Treatment.—The most important part of sporadic cretinism is the specific treatment, based on the experimental work of Schiff and Horsley.

Methods.—Grafting of thyroids, as proposed by Horsley and carried out by Bircher and others, is rarely used. The same may be said of feeding raw or cooked fresh thyroids, which are not always easy to procure and easily decompose. Liquid extracts, or more frequently powders of the dried glands, are used, glands from sheep being official. The official preparations are: Liquor thyroidei, B. P., freshly prepared, 100 minims represent one gland, dose, 5 to 15 minims; Glandulæ thyroideæ siccæ, U. S. P., Thyroideum siccum, B. P., one part equals five of fresh gland; dose, 1 to 5 grains. These are, on the whole, satisfactory, but it must be borne in mind that even when carefully selected they do not always agree in the amount of active principle they contain. A method of standardizing is much needed. Even if standardized it would probably be necessary in each case carefully to observe the effect of the remedy, and adapt the dosage to the individual. The usual beginning dose is one grain of the powder, once or even three times a day, increasing according to the indications or results. The latter are less marked in proportion to the duration of the disease. The effects appear within a few days, usually, but sometimes later. Loss of weight is one of the first signs, then a more natural condition of the skin, with return of secretion of the sweat and sebaceous glands. Cyanosis disappears, the pulse becomes natural, the movements livelier. Sleep is more natural; apathy and indolence lessen. The hair grows rapidly, and becomes fine and glossy; the blood returns to normal. The "natural impulses of growth, which were in abeyance in the thyroidless condition, are let loose" (John Thomson), even at an age when growth has usually ceased, and often equal 1 to 2 cm. a month. The body becomes more shapely. The teeth grow, and the second set are often large and well formed. The development of the mental faculties varies much in different cases. It is most marked in patients under ten years. Some children, under treatment, rapidly catch up with their fellows of the same age in their studies; others remain wholly or partly idiotic.

After the patient has made a definite improvement under the maximum dose, of about 25 grs. a day in some cases, the dose is greatly lessened, or stopped at intervals, until a fairly accurate dosage has been discovered. The temperature is a useful guide in some cases, the object being to keep it about normal. The possibility of thyroidism or of severe symptoms must always be borne in mind, viz., loss of appetite, nausea or vomiting, nervousness, insomnia, rapid emaciation, fever, tachycardia, increased nitrogen metabolism, and extreme restlessness. All patients with myxœdema are much more sensitive to thyroid medication than are normal subjects, children, however, less than adults. Marfan, Immerwohl, Bourneville, and others have observed severe symptoms and even death from ordinary doses. Siegert reports the death of a rickety child aged eighteen months from a

five grain tablet. The thymus was filled with small hemorrhages. In cases of rapid growth under treatment, bow-legs and bending of the tibiæ sometimes occur, events indicating immediate diminution of the dose.

The general treatment is by no means to be neglected. Diet is an important matter, as shown by the changes for the worse in hypothyroid infants after weaning, and by the experiments of Breisacher. Meat is a poison to such persons. Milk, starches, green vegetables, fruit, and cream soups are useful. Fresh air, bathing, and all other elements of healthy life should be provided.

MYXŒDEMA.

Synonyms.—Spontaneous and operative myxœdema; cachexie pachydermique (Charcot, 1880); cachexia thyroidea; cachexia thyreopriva seu strumipriva.

Definition.—Myxœdema is a chronic disease characterized by trophic disturbances of the skin and subcutaneous tissue and by cachexia and mental disturbances, due to loss of thyroid function.

Etiology.—The form of myxœdema most fully understood is that which sometimes follows operations on the thyroid. This was observed in one of the earliest cases of goitre enucleation (Sick, 1867, reported by Bruns in 1888), and in many patients afterward, but not clearly recognized as a symptom complex until after the publications of the Reverdins and of Kocher.[1]

The most important symptoms are mental inertia or apathy and the changes in the skin. In persons who have not completed their growth, all the signs of sporadic cretinism are present. It comes on slowly, usually many months after the operation. It is most intense after complete extirpation of the thyroid in a young individual. There are many degrees of severity, and one form can pass into another. Even severe cases are capable of improvement if the thyroid tissue left behind hypertrophies. Extirpation of four-fifths of the gland is sometimes followed by symptoms, or if atrophy follows a less extensive operation, the same thing will happen. Or the removal of a lingual goitre may be followed by symptoms, if the other portion of the gland is small. When cachexia follows partial extirpation, the condition is usually mild. The celebrated case of von Eiselsberg shows that metastatic neoplasms from a thyroid tumor can lessen the severity of the symptoms. Myxœdema has been known (Czerny) to occur in case of rapidly growing goitre, and to be relieved by extirpation of one-half the gland (Neudörfer). There is a great difference in the proportion of cases of myxœdema following total extirpation, due partly to methods of operating, partly to thoroughness of search among patients. Kocher, by continued observation, found all but one affected, and in that one there was a recidive. The relation of the operation to the myxœdema is put beyond doubt by the large series of experiments on animals.

In non-operative cases of myxœdema the cause is often impossible to discover. Alcoholism, tuberculosis, acute infections, such as typhoid fever, influenza, pneumonia, cholera, and syphilis, have all been considered, and

[1] See the conclusions of Ewald (*Nothnagel's spec. Path. u. Therap.*, Band xxii) and von Eiselsberg (*Deutsche Chirurgie*, Band xxxviii) regarding the question of priority, and the data in the latter and in Lardy's "Contribution à l'histoire de la cachexie thyreoprive."

probably justly. Although the relation of syphilis has been questioned, the observations of Koehler and of Pospelow and the effect of specific treatment seem to leave no doubt. Pel[1] has observed a family in which a syphilitic father had one son with myxœdema, another with acromegaly. In all these cases atrophy of the thyroid, following infection or inflammation, might easily occur. Some would add to the above list, gout, malnutrition, malaria, exhausting diseases, and all kinds of excesses on the part of the parents. Psychic shocks and the accidents in the sexual life of women (postpartum hemorrhages), also rapid childbearing, and the menopause, seem possible causes of myxœdema in the descendants, less obviously, functional nervous disease.

Myxœdema is a disease of adult life. Beginning with the age of fifteen years, an arbitrary line of division between cretinism and myxœdema, there is an increase up to forty-five, then a decrease. The average age in women is thirty-eight years; in men, forty-two. More than half the cases in women occur between forty and forty-five, and in males two-thirds of the cases occur between thirty-five and fifty. Women are more often affected, in the proportion of 7 to 1. Multipara are especially predisposed. Many cases occur among the well-to-do, or at least those not in the poorer classes.

Family predisposition is often recognizable. Myxœdema has been seen in sisters; it is not rarely associated, in the same family, with goitre or exophthalmic goitre. Simple goitre and exophthalmic goitre may precede myxœdema, or the symptoms of exophthalmic goitre may be combined with those of myxœdema as the function of the gland becomes gradually lost.

Myxœdema is rare in the tropics. It occurs chiefly in cold climates; it is common in England and Northern Europe, less so in North America, where Howard[2] found 100 cases reported up to 1905. It is probably more frequent than the reports indicate. Moffitt has collected 83 cases in California. The writer saw only two typical cases in Michigan, and a number that might be classed as abortive or fruste, although it was not possible to demonstrate their true relations by thyroid treatment. In some parts of England it is so common as to be spoken of as endemic, but is rare in Derbyshire, the traditional home of goitre in England. Maxey and Berkeley[3] have shown the existence, previously denied, of myxœdema in negroes. Berkeley's cases were not typical. It has been found in natives of British India.[4]

Pathology.—Myxœdema occurring before the completion of bone growth causes an arrest of ossification, as has been described under cretinism, but limited by the amount of incomplete bone in the body.

The increased thickness of the *skin*, the "solid œdema," was at first considered due to mucin (Ord, Charles, Horsley, etc.), of which some observers found fifty times as much as normal. The condition is now considered due partly to a tissue resembling granulation tissue, containing an increased number of fibrils and nuclei, partly to an infiltration with an amorphous material resembling mucus in the lymph spaces. A similar infiltration has been described in other organs. The cellular infiltration is most marked

[1] *Berl. klin. Woch.*, October 30, 1905.
[2] *Journal of the American Medical Association*, 1907, xlviii, 1226.
[3] *American Journal of Insanity*, 1897–98, liv, 415.
[4] Smith, *Indian Medical Gazette*, 1905.

around the hair follicles, sebaceous glands, and sweat glands. It is not unusual for the thickening to disappear wholly or in part in the later stages of the disease, and the discrepancies of various investigators may be due to this fact.

The *thyroid gland* is almost always reduced in size to one-half or one-fourth the normal; Ponfick found one weighing 4.05 grams. In rare cases it is absent. There is no relation between the reduction of size and the severity of the symptoms. In some cases the gland is enlarged, but it is then always diseased. It is generally pale, tough, and fibrous. Microscopically it shows scattered areas of atrophy of the epithelium, increase of connective tissue, and degeneration of the arteries. If colloid is present it is likely to be altered in refraction and staining reactions. Ponfick saw peri-arterial hemorrhages.

The hypophysis has been found enlarged, or enlarged and degenerated (Boyce and Beadle, Ponfick, and many others). In one case, Ponfick found the hypophysis not enlarged, but completely atrophied.[1] The thyroid was also atrophied.

Symptoms.—These usually develop slowly, from weeks to years passing before the complete picture is produced. The first notable symptoms are sometimes mental, sometimes in the skin. There is in some cases a frequent or constant malaise, with lapses of memory and other psychic anomalies. In others the swelling of the eyelids, dryness and yellowness of the skin, solid œdema, or the gait may first attract attention.

The thickening of the *skin* is usually first noted in the face, especially the eyelids, or in the chin, cheeks, and neck. The appearance is such as to lead in many cases to a diagnosis of nephritis, but the swelling does not pit on pressure, although it feels much like œdematous tissue in some cases. In others it feels like thick but healthy panniculus, obviously out of place. The terms "solid" or "stagnant" œdema seem misleading. The tissue rarely feels like that occurring in long-standing œdema. The skin is sallow or even yellow in color. Over the malar prominences there are red or sometimes cyanotic areas. It is rough or scaly, often greatly thickened over the wrists, hands, and feet, and on the wrists and hands is often wrinkled so as to form a lozenge-shaped pattern, while the fine lines on the normal hands and fingers are more or less obliterated. The skin is dry, and neither exercise nor nervous excitement causes sensible perspiration. Largely from this the electric resistance of the skin is increased. The sebaceous secretion is often absent. Flat warts and pigmented nævi of various sizes and shapes tend to appear in various parts. The forehead is often wrinkled, the eyebrows elevated, in order to raise the heavy lids from the line of vision. The cheeks are flabby, the lips thick, the lower one often everted. The tongue is large and clumsy in its movements. The insides of the cheeks, the soft palate, and pharynx are often swollen and of yellowish color, the mucosa stiff and dense, making swallowing and talking difficult. The ears are swollen. The teeth are often carious, and pyorrhœa alveolaris is common, but both of these depend much upon the patient's habits, and even in otherwise severe cases the teeth and gums may be healthy. The mucous membrane of the nose is also thickened, yellowish, and gelatinous. Curtis[2] has called attention to

[1] *Zeitsch. f. klin. Med.*, 1899, Band xxxviii.

[2] *Journal of the American Medical Association*, 1894, xxiii, 486.

the possibility of the nasal mucosa being the first seat of the peculiar infiltration. The abdomen is large, usually pendulous. The arms and legs are altered in shape in some cases, the legs looking œdematous, but not pitting on pressure. The hands are larger than before the disease began, the fingers thick and clumsy. The name "spade-hand" (Gull) is sometimes suggestive. The hair becomes dry, coarse, and brittle, and falls out rapidly. On the head this often affects the edges of the hairy scalp most, causing the "frontal band alopecia" of D. Walsh or the "cassowary neck." The hair of the eyebrows becomes sparse and harsh, adding to the peculiar appearance of the face. The hair on the body also falls out. The nails are often coarse, brittle, with longitudinal or transverse ridges, but grow with normal rapidity. All the skin anomalies are worse in cold seasons. Soft, gelatinous pads, like fat, appear above the clavicles, on the front of the neck, thorax, or abdomen, or on the genitals.

The symptoms on the part of the mind and nervous system are striking and important. Weakness or loss of memory is almost always complained of, and all the mental processes are slow. Indecision is marked. The patient is often listless or sleepy, and may even act like an animal in winter sleep (Charcot). The disposition is often kind and considerate, slow to anger, but at times showing bursts of rage. Some patients are suspicious; some have agoraphobia. Hallucinations of sight and hearing sometimes occur, and there may be delusions of seeing small animals, usually not voluntarily admitted by patients on account of the fear of being suspected of alcoholism. Insanity may develop, but, as Starr early pointed out, differs from most forms of insanity.

Speech is usually slow, the voice often altered, muffled, or "leathery." The former is ascribed to a central, toxic affection, the latter to the changes in the tissues of the organs of articulation. Patients often show an unexpected garrulity, continuing to talk after the matter on hand has been settled. This may be related to the fact that they often leave the tongue out, after showing it, like patients in stupor. Not only is indolence marked, but any mental or physical exertion, such as reading or housework, quickly becomes a burden. It is difficult to fix the attention, or to carry out a line of thought, but a certain degree of shrewdness may still be retained. The reflexes are weak but rarely absent. Cramps or spasms of the extremities occur; Chvostek's phenomenon can often be elicited. The gait is peculiar, usually weak and somewhat atactic, like that of a person stiff from overexertion. Patients often stumble and find especial difficulty in walking downstairs or on uneven ground. The chief reason for the gait seems to be the thickening of the subcutaneous tissue, perhaps assisted by alterations of the muscles. The head often has a tendency to fall forward or backward, even without drowsiness. Headache is frequent, sometimes suggesting that of nasal disease. Neuralgias and pains in the muscles, joints, and bones are not rare.

The organs of special sense are often affected. The eyelids are swollen, often red at the edges. Use of the eyes causes weariness. Lacrimation is frequently present. Wagner has reported a case of neuroretinitis in which vision was much improved by thyroid treatment. Deafness is a common symptom, and depends usually upon myxœdematous thickening of the mucous membranes in the pharynx or ears. Tinnitus is frequent and troublesome. Taste is often absent, or there may be anomalies of taste, or

PLATE III

FIG. 1



FIG. 2



Myxœdema. Original observation. Woman, aged fifty years.

Hands showing changes under two months' treatment with thyroid extract.

FIG. 3



Myxœdema.

This shows the frontal band alopecia with new hair one-half inch long, the result of two months' treatment with thyroid extract.

a sensation of burning in the mouth, without evidences of irritation. The swelling of the mucosa of the nose is a frequent source of irritation. Cleveland has called attention to swellings on the turbinate bones, of waxy pallor, improved by thyroid treatment.

The sense of touch is reduced where the skin is thickened. The patient is often painfully sensitive to cold, and all the symptoms are usually worse in cold weather. The skin is colder than in health, and the internal temperature is low, generally about 97° or 96° F., sometimes as low as 95° or 93° F; 98° is to be looked upon in such cases as a febrile temperature.

The heart's action is weak, the second sounds sometimes accentuated. The pulse is infrequent, from 40 to 60 per minute, regular, usually of low tension. There is often arteriosclerosis beyond the degree to be expected from the patient's age. The heart may be dilated. Pain in the heart occurs even without thyroid medication. Hemorrhages sometimes occur in the skin and mucous membranes.

The blood shows more or less anæmia in about half the cases, the red corpuscles being reduced to about 3,000,000, sometimes 2,000,000 or less per cmm. The hæmoglobin is reduced to about the same proportion as the red cells; sometimes lower. Normal counts have been noted, and probably exist in cases with high specific gravity of the blood (A. Schneider). Kraepelin and Lebreton and Vaquez described increase in size of the red cells. Nucleated red corpuscles are not uncommon with low red counts. The leukocytes are usually not greatly increased, and show no noteworthy changes in their formula, unless an increased number of large mononuclear cells. Prout has noted large blood platelets.

Loss of appetite is very common, and digestion weak. Thirst is almost never felt. Constipation is often present, but diarrhœa, sometimes profuse and frequent, is not rare. Hemorrhoids are also likely to occur. The urine often shows no abnormality. The quantity is more often diminished than increased. The specific gravity is low. The nitrogen elimination is low. Albuminuria occurs in about one-fifth of all cases; in some of these cases other forms than serum albumin have been reported. Mucin has been found in considerable quantities under treatment. Nephritis, usually chronic interstitial, is comparatively frequent, but glycosuria is rare.

The mucosa of the labia often shows an infiltration like that in other mucous membranes. Leukorrhœa is often present. Menstruation is irregular in many cases. Bramwell[1] has reported the case of a patient, aged thirty-six years, myxœdematous from her twenty-fifth year, who menstruated regularly. Menorrhagia is sometimes marked. In one patient, judging from the history, it seemed to be the first symptom, soon followed by yellow skin, which was not unnaturally ascribed to the loss of blood. Sterility is frequent, but not uniform. Kirk reported a patient who had thirteen children during the disease. Improvement has often been observed in pregnancy. This has been ascribed to the influence of the fetal thyroid (!), but seems more easily explained by the increased nutrition in pregnancy. Hertoghe mentions spermatorrhœa as one of the results in the male.

Many *varieties* of myxœdema can be recognized. Until recently it was supposed that there were two main groups, acute and chronic. The former we now recognize as tetany, but there are some cases of myxœdema that come

[1] *Clinical Studies*, 1903–1904, ii, 329.

on rapidly after operations, or in cases of goitre or exophthalmic goitre, or from unknown causes. Such cases were described by Ord, Charcot, and others. Among these may be placed Osler's remarkable case, reported to the American Neurological Association in 1898, in which a man, aged thirty-one years, had a rapid gain in weight, bloating of the face, enormous enlargement of the abdomen with splitting of the corium, diarrhœa, and irritable temper. Rapid pulse and bloody stools soon followed, with increased tachycardia, delirium, glycosuria, and death. Anders[1] has called attention to similar but less severe cases, suggesting a combination of myxœdema and Basedow's disease.

There are many varieties depending upon the completeness of the clinical picture. Many of these, in fact, are difficult to distinguish from certain cases of neurasthenia, psychasthenia, or senility, premature or otherwise. Hertoghe[2] is the most ingenious and thoroughgoing student of these cases, which have also been investigated by Pel and Buschan.

Myxœdéme fruste, larvate or incomplete myxœdema, is likely to be characterized by such symptoms as apathy, slight thickening of the subcutaneous tissue, flush in the malar regions, a sensation of or tendency to chilling, and a thyroid smaller than normal. Hertoghe would call all of these fully developed cases of myxœdema, and it would be well in all such cases to make a trial with thyroid preparations. He would include among incomplete forms not only all infantile cases, but also such processes as adenoids, hypertrophies of the nasal mucosa, painful swellings of the liver, and varicose veins. It is certainly tempting to consider them, and many other changes, as due to hypothyroidism, and some are latent cases, but there are often contradictory features, and the therapeutic test is not always unequivocal. Another interesting variety is myxœdematous infantilism, a case of which was reported from the writer's clinic by Morris.[3]

According to the severity of the symptoms we can distinguish mild, severe, and intermediate cases of myxœdema. Murray has described a mild form in women aged forty to fifty years, which recovers spontaneously.

Diagnosis.—Myxœdema is easy to recognize if the symptoms are at all marked and the clinical picture borne in mind. The fact that cases are still occasionally mistaken for nephritis or jaundice shows the need of constant effort to avoid such errors by careful and thorough examination. Incomplete cases, and cases under the form of obesity, or lymphangitis, or trophœdema,[4] can only be recognized by careful examination, and usually prolonged observation under treatment.

Prognosis.—Before the thyroid treatment was known the outlook for the myxœdematous patient was hopeless. Progressive increase of symptoms, with relative improvement in summer and relapse in winter, usually brought the patient to a point in which any intercurrent disease proved fatal. Spontaneous recovery of distinct cases was rare, although Fraser reported one after ten years. The average duration was five to seven years. Under thyroid treatment the prospect is very different. In mild cases a practical cure can be obtained, and even in severe cases the symp-

[1] *Journal of the American Medical Association*, 1897, xxix, 63.
[2] *Nouvelle Iconographie de la Salpêtrière*, 1899, xii, 261.
[3] *International Clinics*, 1906, vol. iv, 17th series, p. 132.
[4] Meige, *Nouv. Icon. de la Salpêt.*, 1899, xii, 453; *ibid.*, 1901, xiv, No. 6; Parhon et Cazacou, *ibid.*, 1907, xx, 448.

toms can be so controlled that a symptomatic cure is possible under careful treatment. Death occurs from intercurrent disease, such as tuberculosis or pneumonia, or accident, like uræmia or apoplexy, sometimes from severe intoxication, with nervous symptoms like those already described, and coma or prostration.

Treatment.—This may justly be looked upon as one of the most remarkable achievements of medicine. It is at present the best example of "substitution" therapy or organotherapy, better named opotherapy.

Methods of Thyroid Medication.—The usual method of treatment consists in the use of dried thyroid of the sheep, as mentioned before. Grafting[1] is still used, but has obvious disadvantages. Colloid of thyroid glands, tried by Cunningham (1898) and Buchanan (1899), is not at all promising. Iodothyrin has been tried by many, but is less effective than the dried gland. There is rarely any difficulty in getting patients to take the tablets, so that the rectal and inunction methods have no advantages. "Thyroidoerythism" of Poncet (1894), irritating the thyroid by means of iodoform plugs or foreign bodies, need only be mentioned as an example of the pains taken by some to avoid simple treatment.

The beginning *dose* is usually one tablet (2 grs. of dry powder) three times a day. Some patients can not take this dose, but may begin with one tablet a day, or even less. Usually the larger dose can be taken, and increased up to five or six tablets daily, until a good result has been secured. The dose is then cut down, and the final amount determined by careful experiments.

The effect of the treatment is quickly evident, both on the physical and mental symptoms. There is rapid and marked loss of weight, greater in the early days of treatment and due to the loss of myxœdematous infiltration and of fat. The loss of weight may amount to twenty or thirty pounds, or more. The face becomes thinner, the eyelids lose their puffiness, and the eyes may even seem to recede into the orbital cavities. The malar flush disappears, and the cheeks take on a youthful pink. The fat pads disappear, the body and extremities shrink. Smaller gloves and shoes can be worn, and the stiff gait and inability to bend the body subside. The skin loses its harshness and dryness within a few days. Sweating returns and may be profuse and offensive. Menstruation reappears. Bramwell saw milk secretion in one case. The urine is increased in the first few days, but soon falls to the previous quantity. Talking and swallowing become easier. The memory improves, the mind becomes clearer, endurance and initiative return to normal. The hair begins to grow again, although the former hair continues to fall out. The hair has its natural color, even at advanced age.

The best results occur in cases with most swelling. As an example, in Kinnicut's case, the first one treated in the United States (1892), the woman had been ill for twelve years, was bedridden, deaf, and hairless, with intense mental and physical prostration. There was marvellous improvement within a few weeks; hearing became normal, hair grew down to the waist, the skin was of brilliant color and texture, and the patient, taking 5 grs. of fresh thyroid twice a week, was able to carry out important functions. Age is no obstacle to the result. Bramwell had a successful case at 69 years, after years of illness. The blood at first becomes more anæmic,

[1] Cristiani, *La Semaine Médicale*, 1904, No. 10.

and then improves. Even growth of the skeleton may begin at ages beyond the usual period.

Important symptoms may occur during treatment, and must be carefully guarded against. F. C. Shattuck early pointed out the occurrence of cardiac pain with frequent pulse, elevation of temperature, and other symptoms. This has frequently been seen, and has led many to insist on the patient remaining in bed in the early weeks of treatment. If this is not done, the patient should be put to bed on the occurrence of any of the symptoms mentioned, the dose of thyroid cut down or stopped altogether, and ice-bags, strychnine, or cardiac stimulants used. At later periods such symptoms may occur even from small doses. Thus, Bonney observed exhaustion after 4 grs. Bramwell[1] saw distinct symptoms on taking one-half of a tablet, equal to $\frac{1}{128}$ of a gland. Putnam pointed out the occurrence of heart weakness long after thyroid treatment, and Murray saw a death from exertion, but, on the other hand, many patients become able to carry out considerable effort, as in mountain-climbing. Other toxic symptoms are: Delirium, somnolence, spasms, dyspnœa, albuminuria, glycosuria, pain in various parts of the body, erythema, or urticaria. Diarrhœa occurs in some cases, with or without nausea and vomiting. Thyroid extract is much more toxic to myxœdema patients than it is to healthy persons. The early idea, that the toxic effect is due to decomposition, is not much held at present.

The skin usually quickly becomes healthy, but in some cases desquamation takes place in large areas, especially on the hands and feet. Foerster reported a chloasma-like eruption on the temples and forehead during treatment. He also saw abscesses form in the skin in places where camphor had been injected forty days previously. Œdema of the legs often follows the disappearance of the myxœdematous swelling.

In some cases there is a paradoxical condition. Larger doses of thyroid become necessary for the myxœdema symptoms, but the toxic phenomena are as severe as ever, as one of Ewald's patients observed. Atrophic cases are more prone to symptoms of depression, and these patients should be kept in bed in the beginning of treatment. Ewald recommends arsenic, in the form of Fowler's solution, three drops a day, as a preventive of symptoms of thyroidism.

During treatment, and after improvement has been obtained, the general condition should be carefully treated. The diet should be simple. Meat should be excluded or reduced to the minimum; milk, vegetables, cereals, fish, and fruit are permitted. Alcoholics are injurious. The patient should avoid severe cold, but should be in the open air as much as possible. Bathing and exercise must be adapted to the effects. Cold baths are never well borne.

[1] *Clinical Studies*, 1903, ii, 261.

CHAPTER XIX.

THE PITUITARY BODY. ACROMEGALY. PROGERIA.

By GEORGE DOCK, M.D.

THE PITUITARY BODY.

The pituitary gland or hypophysis cerebri is a body of variable size, 6 to 10.5 mm. in sagittal, 10 to 14.5 mm. in vertical, and 5 to 9.75 mm. in transverse diameter (Zander), and weighing on the average, in health, 0.6 gram. It lies in the sella turcica or pituitary fossa of the sphenoid, attached to the base of the brain, behind the optic chiasm, by the infundibulum.

It is composed of two lobes. The larger or anterior lobe is made up of follicles of various shapes, containing large "chromophile" cells with both "acidophile" (eosinophilous) and basophile ("cyanophile") granules, and smaller paler cells of indistinct outline, called "chief cells" (Stieda), "granule masses" (Rogowitsch), "granular protoplasm" (Schoenemann), or "chromophobe" cells. According to Benda, accepted by others, the various cells represent stages of a single class, the chromophile cells being more numerous in middle life, the chief cells in old age. Erdheim has shown the existence in the cells of fatty granules, which become larger and more numerous with age. In older subjects some of the follicles contain a material like thyroidal colloid, which also occurs between the follicles.

The posterior lobe is made up of connective tissue, bloodvessels, pigmented cells of various sizes and shapes, and also cells like those in the anterior lobe. Between the two lobes is the "pars intermedia," a partly vascular, partly glandular structure, with colloid in tubules and vesicles. The two lobes have separate blood supplies. The capillaries of the anterior lobe are "sinusoid."

The anterior lobe is derived from Rathke's pouch of the pharyngeal entoderm, the posterior lobe from the midbrain ectoderm. It is unnecessary to detail the results of investigations in the physiology of the pituitary, since they are still unsettled. A resemblance of the structure of the gland to that of the thyroid had long been known, and Rogowitsch, Stieda, and others found enlargement of the pituitary after thyroidectomy, involving the chief cells, and suggesting compensation. Bourneville, Osler, Compte, Ponfick, and others found enlargement in cretins. Schoenemann and Compte obtained divergent results in their examination of the pituitary in cases of thyroid degeneration. Compte saw hyperplasia, corresponding to the results of experiments. Oliver and Schaefer found a blood pressure raising substance which Howell thought was produced by the posterior lobe, but Herring recently brings evidence suggesting its origin in the pars intermedia. Schaefer and Vincent found a depressor substance (1899). Rinon and Delille think extract of the posterior lobe stimulates the adrenals and lessens thyroid function, and that extract of the anterior lobe increases thyroid function. The results of extirpation of the gland vary in detail,

according to different investigators. Masay (1906) claims to have produced a pituitary cytotoxin which causes cachexia and deformities of the extremities in dogs.

According to experiments of Schaefer (Herter Lectures, 1908), many difficulties are due to the complex function of the gland, and it is probable the relation of the pituitary body to other organs and to diseases, concerning which so many brilliant speculations have been made,[1] is closely associated with the production, by various parts of the pituitary, of "hormones," "activating" or stimulating substances with obscure but important effects on numerous organs, ductless, sexual, and others, as well as upon metabolism in its broadest meaning, including growth.

Pathology.—Circulatory changes, from anæmia to hemorrhage, are very frequent in the pituitary. Postmortem changes occur quickly, and have caused much confusion. Colloid and cystic degeneration are not rare; softening cysts, fibroid degeneration, and calcification are also not uncommon findings. Combinations of degeneration and hypertrophy of the gland are important, the latter giving rise to the adenoma or so-called struma of the pituitary. These may reach considerable size, cause pressure on the brain or optic chiasm, or erode the bones. According to C. Löwenstein,[2] they are frequent, especially in adults; are not characteristic of degenerated, but of developing organs, and should not be unexpected in cases of acromegaly.[3]

The numerous tumors described as sarcoma and carcinoma of the pituitary have in some instances been adenomata. Cases of undoubted sarcoma have been observed, as also carcinoma. In some cases of the latter, with metastases, defective development of the sexual organs has been observed. Acromegaly is not always present. Kollarits has collected 50 cases of tumor without acromegaly. Gummata, tubercles, and echinococcus have also been noted, and also without acromegaly. Teratomata and lipomata have been described. Various explanations have been given for the cases of pituitary tumor without acromegaly, such as age beyond the period of overgrowth, or different histological structures in the two classes of cases. Serious doubt may be given to reports of cases of acromegaly in which the gland is reported normal. Bregmann and Steinhaus[4] assert that in all cases coming to autopsy there has been some alteration of the pituitary. Benda's investigations, as those of D. D. Lewis,[5] go far to confirm this. In a case of acromegaly with no macroscopic lesion of the gland, Lewis found an increase of chromophile cells and loss of chromophobe. Some cases of acromegaly with malignant disease have had a rapid course.

ACROMEGALY.

Synonyms.—Acromegalia; acromégalie (Fr.); Akromegalie (Germ.); Pachyacrie (von Recklinghausen); Marie's disease.

[1] See especially F. Pineles, *Die Beziehungen der Akromegalie zum Myxœdem und zu anderen Blutdrüsenerkrankungen, Samml. klin. Vorträge,* 1899; Sajous, *The Internal Secretions and the Principles of Medicine.*

[2] *Virchow's Archiv,* 1907, clxxxviii, 44.

[3] Swale Vincent, *Internal Secretions and Ductless Glands. Lancet,* 1906, ii, 348, 430.

[4] *Virchow's Archiv,* 1907, clxxxviii, 360.

[5] *Johns Hopkins Hospital Bulletin,* May, 1905, xvi, 157.

Definition.—Acromegaly is a chronic disease characterized by an abnormal increase of the size of the extremities and of some internal organs, with cachexia, associated with morbid function of the pituitary gland.

History.—Knowledge of the disease began in 1886, when Pierre Marie described two cases of his own and others in the literature, and distinguished it from other diseases with some of the same symptoms. At once various accounts of similar or related cases were sought out in the older literature, including some described as "macroglossia" or big tongue. An important preparation for Marie's announcement had been made in 1872, by Carl von Langer's anatomical study of giants. In that, von Langer had described two types of giant crania, one normal, large but well formed, the other with a large sella turcica and enormous lower jaw, with other features now well known as acromegaly. He also pointed out the enlargement of the soft parts, and from the alteration of the sella turcica concluded there had been degeneration of the pituitary body. The work of Fritsche and Klebs (1884) brought a serious confusion into the subject. After Marie's first publication wide interest was aroused. He himself added to the literature in 1888, and in 1890 his pupil, Souza-Leite, gave an exhaustive study.[1] Among the numerous important works may be mentioned those of Collins (1892), M. Sternberg (1894, 1897), Brooks (1898), and O. T. Osborne (1892, 1897, 1899, and in the *Reference Handbook of the Medical Sciences*, 1900, vol. i). Interesting references to early literature are given in the study of Felix Patry, *L'Acromegalie avant*, 1885, Paris, 1908.

The prescientific history of acromegaly is intimately related to the literature and folk-lore of giants, especially the deformed and monstrous kinds. The sculptures of many French and Italian Gothic churches show interesting examples.[2]

It is not necessary in a work of this kind to speak in detail of giants, although they belong more to medicine than to anthropology. The current idea of a giant is probably that of Geoffroy St. Hilaire—"an individual superior in size to that of the race," but this is too general. Meige (1902) made a useful classification into normal and pathological giants, the former rare, the latter less so, which agrees in general with the division of von Langer, but is more accurate in detail. Anthropologists make an arbitrary classification, those above 2 meters (6 ft. 8 in.) in height being termed giants. Clinically it is more accurate to make a further classification, and we can, with Roy, speak of transitory or precocious giants, such as occur sometimes at puberty, infantile giants, resembling eunuchs and castrated animals in many particulars, and acromegalic giants. The giantism may be partial, affecting any part of the body. Sometimes the fat is hypertrophied. It is not always easy to distinguish accurately the various classes. Some individuals looked upon as true giants have proved to be acromegalic. So far from being superior creatures, as is often thought, even the most "normal" giants are physically and functionally defective in many ways. They are relatively and sometimes absolutely weak; they often have large or deformed extremities, even if not clearly acromegalic; they are all mentally inferior, furnishing "more drum-majors than Academicians"—and all die young, usually between twenty and thirty.[3]

[1] Essays on Acromegaly, by Pierre Marie and Dr. Souza-Leite, *New Sydenham Society*, London, 1891.

[2] Jean Hirtz, *Nouvelle Içonographie de la Salpêtrière*, 1908, p. 90.

[3] See Launois et Roy, *Étude biologique sur les Géants*, 1904.

Etiology.—Acromegaly is a rare disease. Benda, in 8000 autopsies, encountered 3 in 13 months, and only one more in seven years. It has been found in all parts of the world, among all races. Berkeley described the first negro case, Dana that of an American Indian. The two sexes are about equally disposed to the disease.

Acromegaly occurs most frequently in the third decade of life, very rarely in the second or after the fourth, although in women it seems to begin, on the average, later than in men. Moncorvo's case in a child aged fourteen months, is considered not acromegalic, probably cretinous. It affects especially people of large size. According to Sternberg 20 per cent. of acromegalics are above six feet in height when symptoms begin, while 40 per cent. of giants are acromegalic. Dwarfs, however, are not immune. A family predisposition has been noted; also diabetes in the ascendants and goitre in the patient or immediate relatives. Among the causes assigned we find inherited nervous disease, alcohol, lead, syphilis, emotional shock, such as fright, various infectious diseases, typhoid and scarlet fever, poisoning by illuminating gas, and trauma. In Perry's case (1905) with a history of trauma, it seems the condition was a not unusual form of local hypertrophy rather than acromegaly. Very often the history or an old photograph will show that the disease antedates the alleged cause, although the latter may sometimes hasten the progress of the disease.

Pathology.—It was supposed at first that acromegaly was due to lack or suppression of the internal secretion of the pituitary, but more recent histological and experimental work indicates that hyperfunction is more probable, and that altered function of other ductless glands, including the internal secretion of the sexual glands, have important but as yet obscure relations to the disorder of nutrition that causes so many of the striking features of the disease. Some of the reasons for this view have been given in the preceding section, and others will appear in the following.

Morbid Anatomy.—*Bones.*—Although the enlargement of the extremities is usually the most striking anatomical alteration, all the bones of the body are more or less affected. As in the extremities, however, the process is not a general enlargement, but an exaggeration of bony prominences, crests, ridges, tuberosities, etc. The grooves for tendons, vessels, and nerves are often of unusual depth. The process is due to periosteal growth, and osteophytes are common. The bones are often increased in density in the outer parts, but the spongy portion is often lighter than normal. Hans Curschmann calls attention to degenerative processes, causing atrophy of the bones of the hands and feet. He found this in three cachectic cases. Among the individual bones some show alterations that deserve particular mention.

The cranium is often deformed by osteophytes and a great exaggeration of the occipital, mastoid, and other prominences. The orbital arch is large, the frontal prominences conspicuous, the zygoma, malar and nasal processes all increased in size. The glenoid fossæ are larger and wider apart than normal. The lower jaw is almost always enlarged in all directions. The cranium is usually irregularly thickened, and is remarkable in most cases for the enlargement of the sella turcica. The sphenoidal sinuses are large, the antra of Highmore also, as are all the accessory sinuses. The vertebral column is always deformed in advanced cases, with kyphosis of the cervical and upper dorsal regions. The vertebral bodies are not altered, except secondarily, but the processes and borders are enlarged.

The most striking alteration is usually in the extremities, viz., enlargement of the hands and feet, but with the exception of the terminal phalanges, which are often broad and thick, with exostoses in variable size and number, the bones of the extremities are rarely really enlarged. If they are, the process is not considered essential to acromegaly.

Skin and Subcutaneous Tissue.—Examinations postmortem show that the enlargement of the extremities is not chiefly bony. *X*-ray examinations show the same thing, as described by Schultze, Schlesinger, Edel, and others. It is therefore more accurately described as pachyacria than acromegaly. The subcutaneous tissue is thickened by connective tissue growing in and around the fat lobules, sometimes forming fibrous tumors. Similar growths surround the sweat glands and nerves, or sometimes pass between the nerve fibers. The hair follicles, sweat glands, and bloodvessels in the skin are not notably altered. The connective-tissue overgrowth also occurs in the muscles.

The *pituitary gland* is often enlarged, as it was in the early case of Verga (1869) and in von Langer's pathological giants. Sometimes the gland is described as normal, but obviously enlarged beyond the average. Sometimes the enlargement is only moderate, up to the size of a cherry, but with erosion of bones, indicating abnormality. It may reach the size of an apple, growing down to the pharynx, or up into the base of the brain, and outward into the lateral sinuses. The anterior lobe is especially involved. Of the alterations described, the most frequent are: hyperplasia or adenoma, cystic, fibrous, "malignant" adenoma, sarcoma. Hanau showed that the so-called sarcomata are derived from the epithelium of the gland, so they are better named malignant adenomas. Benda found in his four cases an excessive number of chromophile cells. He thinks the hyperplasia of functionating cells is present in all cases of acromegaly, but that in the further course of the disease either a malignant degeneration of the hyperplastic tissue, or some other tissue, replaces the functional cells.

The other ductless glands show no constant change. If altered, the condition is not always easy to distinguish from a complication. The adrenals have been normal or slightly atrophied. The thyroid gland is almost always abnormal, being either large and goitrous or atrophied. In a case in the writer's clinic, Warthin found the parathyroids hyperplastic, weighing 1.5 to 1.7 g., with cystic dilatation of the lymph spaces. The thymus is often enlarged. Benda found the carotid glands small, but normal. The pineal gland has been found enlarged. The dura and pia arachnoid are sometimes calcified or even contain bony plates not, of course, peculiar to acromegaly. The brain is sometimes described as large. The most important changes are those due to pressure, especially in the region of the infundibulum, chiasm, and pons. Various degenerative changes have been found in the spinal cord. The peripheral nerves are sometimes affected as already described. Barrett has reported an interesting case. Degeneration of the cervical sympathetic has been described in some cases. In many others it was normal.

Enlargement of internal organs, or "splanchnomegaly," has been described, involving especially the kidneys, liver, heart, and spleen. In one of Osborne's cases the heart weighed forty-one ounces. The pericardium is sometimes thickened.

While the external genitals are usually hypertrophied, the uterus, ovaries, and testes are often hypoplastic or degenerated.

The pancreas is sometimes the seat of connective-tissue overgrowth, but shows no constant specific diabetic change, even in cases in which diabetes was present during life (Benda).

Symptoms.—The acromegalic patient is usually able to give a history of important symptoms long before the characteristic deformities occur. Headache, frontal or vertical and often excruciating, irritable temper, moroseness, pains in various other parts of the body, including the joints, disturbances of vision, loss of memory, tingling or numbness of the extremities, increased appetite and thirst, constipation, polyuria, and various dyspeptic symptoms, are the most frequent early phenomena. In women amenorrhœa is frequently but not always noted; in men, sometimes, loss of sexual power. Variations in the course of the symptoms can often be discovered, and sometimes a gain in weight. If besides some of the symptoms noted there is a statement of increased growth, either general or in the "ends" of the body, suspicion should at once be entertained that the case is one of acromegaly. A comparison of old photographs will often assist in showing the changes of the extremities, but as Benda has pointed out, care must be taken to avoid mistake by the perspective errors common in photographs. Changes in the sizes of hats, gloves, and shoes are more trustworthy. The latter may increase two or three sizes. Sometimes the abnormal growth begins before the subjective symptoms, but is not considered a sign of illness.

The head shows unusually arched and prominent brows, with the forehead retreating. In one of the writer's adult cases the hat-size changed from $6\frac{7}{8}$ to $7\frac{7}{8}$. The skin of the forehead is wrinkled. The nose is large, sometimes enormous. The nasal mucosa is often thickened. Epistaxis is a frequent symptom. The zygomas and malar prominences are exaggerated. The upper jaw is seldom notably altered, although the antra of Highmore are enlarged. The upper lip is often long and thick. The lower jaw is almost always enlarged, although in some otherwise typical cases (Gauthier, Campbell, Whyte) it has not been so. The bone is enlarged in all directions, so that the condyles are farther apart than normal, the rami longer and wider than normal, the symphysis thicker and uneven. The lower teeth may be 2 cm. or more beyond the upper ones. The alveolar process is, as it were, rolled out, the teeth farther apart than normal, "enlarged" in one case. The face is generally oval ("type ovoide" of Marie, often spoken of as prognathous, but not strictly so, and more accurately spoken of as progenic ("cranium progenicum"). When the jaw is not prominent the face is spoken of as square ("type carrée" of Marie). The chin is thick. The head tends more and more to lean forward, and the chin may come to rest upon the sternum.

The eyes may be of normal size and position in the large orbital cavities, or there may be exophthalmos from bony growths or increase of soft parts in the orbit, or even actual enlargement of the bulbs. The lower eyelids are often thick. The ridges in the occipital region are usually much increased in size. The tongue is almost always large, although Dreschfeld saw a case with large lower jaw and tongue of normal size. It may be so large as to force the mouth open, and it plays a part in the deformity of the alveolar processes. The tongue is usually indented at the sides, fissured, and the papillæ enlarged. The soft palate and uvula are often thickened.

PLATE IV



Acromegaly. Original observation.

The size of gloves changed from 6 ¼ to 8½, and of shoes from 3 to 5½.

The larynx is sometimes large and its mucosa thickened generally or in various parts. Corresponding to the changes in the mouth and larynx, the voice is often affected, deeper in pitch than before, and speech is slow and thick. The submaxillary, salivary, and cervical lymphatic glands are often enlarged; the thyroid is sometimes goitrous, sometimes atrophied.

Kyphosis, kyphoscoliosis, and lordosis are present in various degrees, sometimes observed early, usually increasing in the advance of the disease, and causing a marked decrease in height. The thorax is often large, especially in the anteroposterior diameter, the ribs are often thickened at the ends, their motions interfered with, and respiration largely abdominal as a result. The sternum is enlarged, thick, and uneven. The spinous processes of the vertebra are often much enlarged. The clavicles are generally thick and sometimes enlarged in all directions. In comparison with the size of the thorax the abdomen often looks small, and is rarely pendulous. The pelvis is often enlarged by bony growths on the crests and tuberosities of the bones. Enlargement of the clitoris, labia, and penis, and reduction in size of the uterus, ovaries, and testes have been mentioned.

The shoulder joints are sometimes large, also the elbows, but the forearms are often thin and weak, and look still smaller on account of the increased size of the hands. The latter occurs under two different forms. In one the hand is long ("type en long," or giant type of Marie), more frequently broad ("type en large," or massive) and paw-like. The fingers in this type are thick, sometimes clubbed at the ends, sometimes "sausage-shaped." The skin of the hands is thick, the subcutaneous tissue also. The nails are often short, thick, brittle, and striated. Although the bones of the hands and fingers are sometimes increased in length, most of the enlargement comes from the increase of the subcutaneous tissue, with exostoses and increase of the points of attachment of the tendons.

The knee-joints are sometimes enlarged, also the patellæ. Crepitus may be present in the joint. The ankles and feet show a more decided enlargement. The enlargement of the os calcis backward, and of the great toe, and an enlargement of the outer side of the foot cause a very characteristic feature of the disease. The skin and soft parts of the feet show alterations like those of the hands. The subcutaneous tissue in general is often thickened by connective-tissue overgrowth. Later this is followed by atrophy. The skin in general is often yellowish or brown. Over the nose it is sometimes red, with enlargement of the sweat and sebaceous ducts. The skin is usually dry, but perspiration is easily provoked. The hair usually grows well. It may be increased on the body. Nævi, mollusca fibrosa, fibromas, sometimes painful, and lipomas often occur in the skin. Flushing, tingling, sweating, and other vasomotor changes in the skin are frequent. Hemorrhoids and varicose veins are not rare. Verstraeten observed high fever, but, as a rule, the temperature shows no marked alteration.

The muscles show no marked change in the early stages or may be increased in size and strength. Later they become small and weak, a change that has much to do with the peculiar way of holding the head, and the kyphoscoliosis and other deformities. Great weakness may occur temporarily in various muscles.

The pulse is rarely accelerated. The heart usually becomes hypertrophied. Later, dilatation and loss of compensation, with great œdema, become important factors in the case. Sclerotic changes in the bloodvessels are

often present. Dyspnœa is frequent, from weak heart or from the changes in the bony thorax.

The liver and spleen are often papably enlarged.

Many of the nervous symptoms in the disease are directly due to the pituitary tumor so often present. Uhthoff[1] has explained why pressure symptoms are not still more frequent. Ward Holden (1900) has described the mode of involvement of the optic chiasm. The diaphragm of the sella turcica prevents enlargement forward for a time. Affections of the oculomotor nerves occur when the tumor grows backward; if it increases sideways the abducens becomes affected. Affections of the sight occur in more than half the cases. Blurring of vision, concentric narrowing of the visual fields, bitemporal hemianopsia, and optic atrophy with amblyopia to amaurosis are encountered. The pupils are generally normal, but may be dilated. Nystagmus and strabismus occur. The retina is often congested. In some cases only one eye is affected.

The external ears are often large and thick. Deafness is not infrequent, and from pressure on the cavernous sinuses, tinnitus aurium is frequent and often painful, especially on lying down. The external auditory canal is sometimes enlarged, the membrana tympani thickened. Smell and taste are rarely affected. Paræsthesia of the extremities is a frequent symptom. The tactile sense is sometimes lessened in the hands and feet. The reflexes are not notably affected in most cases. Beduschi has reported a case in which the knee and Achilles reflexes were absent, and with amyotrophic palsy and alterations of faradic excitability.

Loss of memory, slowness of mental processes, and depression or delusions are frequent. Bursts of anger are likely to occur, or insanity with suicidal or homicidal tendencies. Epilepsy is sometimes combined with acromegaly as described by Farnarier and also Shanahan. Somnolence is often a marked symptom, and may pass into stupor. Vertigo and syncope are not unusual. Part of the nervous symptoms are due to pressure, but others depend upon more indirect causes, toxic, circulatory, or from pain, weakness, or the exhaustion from complicating diseases like diabetes, nephritis, or myocarditis.

The blood becomes affected in the later stages, showing low coloring matter, diminished red cells, slight leukocytosis, and a relative or absolute lymphocytosis. Franchini observed lipæmia even in non-diabetic cases, and an excess of calcium and magnesium. Hæmoglobinuria has been observed by Chvostek, who looks upon it as the result of a vasomotor anomaly due to pituitary disease.

The urine shows no characteristic change. A very frequent occurrence is glycosuria, the cause of which is still unsettled. Benda found it without alteration of the pancreas. That it is cerebral and due to the pituitary disease seems borne out by the fact that diabetes is most marked with the largest tumors. Borchardt,[2] in reports of 176 cases of acromegaly, found diabetes noted in 63, and alimentary glycosuria in 8 more, indicating a lack of carbohydrate metabolism in 40.32 per cent. of all cases. Experiments on animals gave support to the view that the symptom was caused by hyperfunction of the pituitary gland. Albuminuria with casts occurs as part of a complicating nephritis in many cases.

[1] *Berl. klin. Woch.*, 1898, Nos. 22, 23, 25.
[2] *Zeits. f. klin. Med.*, 1908, lvi, 332.

The metabolism of acromegaly is not characterized by constant changes in any respect, judging from the few reports in the literature. Bulimia, diabetes, Basedow's disease, and myxœdema cause modifications, as might be expected, when they occur with the disease. Edsall and Miller[1] concluded there was retention of phosphates in the bones and muscles, and increase of urinary calcium. They point out that the metabolism suggests metabolic abnormalities rather than mere overgrowths, so that further researches in the same field are urgently indicated. Feeding with large quantities of pituitary tablets also has little effect, either in health or in acromegaly (Salmon, Magnus-Levy, Schiff, Franchini).

The *course* of acromegaly is very variable. The early subjective symptoms are usually long misunderstood. The remissions of the disease add to the confusion, so that a sudden increase of symptoms following some acute illness or an accident first calls attention to the nature of the process. The remissions may last many months or even years. The duration is obviously difficult to estimate. The usual classification as regards duration includes three forms: Benign, with mild symptoms and a duration up to fifty years; chronic, lasting from eight to thirty years; acute or malignant, ending in six years. The majority of cases belong to the chronic form. Sternberg has called attention to malignant cases, with enlargement so rapid that it can be seen by the physician. In all the cases observed there was malignant disease of the hypophysis. Other varieties are based upon individual clinical features. Duchesneau has called attention to an amyotrophic, Sainton to a neuralgic, and Beduschi to a paralytic form. The terms "pseudo" and "fruste" have been applied to cases with very atypical features. Some of those will be considered in connection with diagnosis.

Acromegaly is often combined with some or many symptoms of other diseases, especially exophthalmic goitre, syringomyelia, myxœdema, and epilepsy. Horsley,[2] in fact, looks upon epilepsy as one of the common features of pituitary tumor.

Diagnosis.—The diagnosis in a typical case is very easy. In the early stages it may be difficult, and it is also difficult to exclude from acromegaly certain examples of various diseases that in some respects resemble it, especially all those associated with local enlargements of the extremities. Brain tumor, arthritis deformans, Graves' disease, diabetes, and progressive muscular atrophy have been supposed to be present alone in many cases, although the whole history and physical condition, if carefully investigated, would quickly reveal the true state of affairs. Acroparæsthesia, especially at the time of climacteric, has been supposed to be present, and until enlargement of the "ends" reveals the true condition the mistake might be difficult to avoid.

It is essential to realize that enlargement of a single extremity or of all the extremities is never enough for a diagnosis. The enlargement of the other ends of the body is much more important, and there must also be some of the nervous, eye, or subjective symptoms. The recognition of a brain tumor in any case, with a localization at the base of the brain and near the chiasm, would lead one to look for disorders of growth, so that the differential diagnosis of the former need only be referred to here. It is important to

[1] *University of Pennsylvania Medical Bulletin*, March, 1903, p. 143.
[2] *British Medical Journal*, 1906, i, 323.

consider some of the diseases that from deformity may be wrongly classed with acromegaly. Myxœdema has frequently been so mistaken. The skin and the mental condition are often much alike in the two diseases. The absence of bony enlargement, the thick myxœdematous pads, the loss of hair, and low temperature are important signs. Cases of myxœdema combined with acromegaly require careful weighing of all the signs, as well as investigation of the less obvious features of both diseases. The confusion with cretinism can hardly stand a careful investigation of the early history.

Erythromelalgia has been mistaken for acromegaly, but a careful examination would prevent error, by disclosing the marked vasomotor feature of the former, and the absence of the characteristic features of Marie's disease.

Giantism is to be differentiated by the absence of acromegalic characteristics. These should be looked for in all giants, especially when changes of figure or other signs of illness occur. Giants with unsymmetrical lesions of bone, from local disease or syphilis, must be distinguished by attention to the general rules.

Osteitis deformans (Paget) differs from acromegaly in the absence of enlargement of the soft parts, the tendency to curving of the tibiæ and other long bones, the more advanced age of onset, the greater tendency to unsymmetrical enlargement, and the absence of the enlarged lower jaw.

Arthritis deformans is sometimes associated with great enlargement of the feet, less frequently the hands, although the great size and thick fingers and toes of acromegaly are not usual in the former. Kyphosis is sometimes present. The two diseases may be combined, in which case, as in others of difficulty, the course of the disease, the subjective symptoms and the condition of the soft parts would be of great importance.

Pulmonary osteo-arthropathy is to be differentiated by the presence of or history of bronchitis, emphysema, or other disease of the respiratory tract, the absence of enlargement of the soft parts of the hands and feet, and the curved nails at the clubbed ends of the fingers and toes.

Hyperostosis may cause serious difficulty in diagnosis, either in leontiasis ossea, affecting the cranium alone, or in the diffuse form. The disease usually begins in early life, may cause deformities of the vertebral column, with exophthalmos, blindness, deafness, imbecility, and death. It may be combined with acromegaly. Cases of this kind cannot be understood until the whole subject of growth is cleared up.

The clinical diagnosis of the various partial overgrowths of fingers, toes, etc., cannot often be made without an accurate idea of the nature of the morbid process, which may prove to be related to acromegaly. All these cases need to be investigated with reference to the pituitary and other ductless glands.

Adiposis dolorosa, multiple enchondroma, elephantiasis, lymphangitis, scleroderma, and trophœdema have at times caused difficulty in diagnosis. Thorough examination alone can prevent serious errors.

The value of skiagraphic examination of the bones of the extremities and of the skull must be remembered, and use made of it for diagnosis as well as for study.

Prognosis.—This varies with the determination of the variety, the presence or absence of complications on the part of vital organs, and the possibility of giving the patient all the care a disease so rich in symptoms requires. Œdema of the brain, uræmia, severe heart weakness, and severe

diabetes are most serious signs. Cases in which an early operation on the pituitary can be successfully performed may enable the prognosis to be modified, but it is too early to foretell the ultimate result in such cases.

Treatment.—Efforts to treat acromegaly with extracts of the pituitary and thyroid have been made by many, but, on the whole, with disappointing results. At the same time, further experiments with organic preparations are legitimate, and the progress of discovery in the physiology and pharmacology not only of pituitary extracts, but of those of other organs, should be carefully followed in order to learn indications of value. Thyroid extract may be useful in cases with myxœdema symptoms, and should be used, with proper care, in such cases. While many have had bad results from pituitary extract, Osborne's experience is interesting and encouraging. Giving from six to twelve grains a day, he saw improvement of many symptoms and of the hypertrophies.

In case a pituitary tumor can be recognized, an effort should be made to treat it surgically, especially if the pressure symptoms are severe. Schloffer, Mozkowicz, von Eiselsberg, Hochenegg[1] and others have shown how much can be accomplished in certain cases. In recent operations the nasal route has been preferred to the frontal, sometimes assisted by *x*-rays. Not only improvement of tumor symptoms, but also diminution of the enlarged parts and of the subjective symptoms, have been obtained. Horsley has pointed out that in such cases "the first duty of the surgeon is to relieve mechanical pressure; to do it so as to avert blindness, and to prevent a fatal result."

The symptomatic treatment must be directed to the relief of symptoms and complications. Analgesics and sedatives will often be required for painful conditions. Diet can often be arranged so as to improve constipation or glycosuria. Potassium iodide, mercury, and arsenic have been thought of benefit. Cardiac weakness, nephritis, and symptoms associated with them must be treated as under other circumstances.

PROGERIA (MICROMEGALY).

Hastings Gilford has proposed giving the name "progeria" to a remarkable condition observed, in one of the cases he studied, by Hutchinson, and noted as a rare freak by earlier writers. In the elucidation of diseases of the ductless glands, and especially of the pituitary body, this condition will probably have its true character assigned. Gilford's[2] cases are so fully described and his conclusions so carefully drawn that it is impossible at present to do more than give the results of his work. He studied three cases: one, a male, coming to autopsy at seventeen; one dying about the same age without autopsy; another, a female, less thoroughly investigated, dying at forty-three.

The clinical features are remarkable for the combination of incomplete development and premature old age. It differs from so-called normal senility in the early age at which it appears, from the great majority of cases of premature senility in not having any of the usual causes, and therefore,

[1] See Schloffer, "Zur Frage der Operation an der Hypophyse," *Beit. zur klin. Chir.*, 1906, Band l, p. 767; Hochenegg, *Cong. f. Chir.*, 1908; Stumme, *Arch. f. klin. Chir.*, 1908, lxxxvii.

[2] *The Practitioner*, 1904, lxxiii, 188.

at present, seems to represent a condition such as can only be explained as the result of some as yet unknown disease of the organs presiding over development. We see the figure, the face, manner, and apparently the ideas of an old man or woman, with the baldness, gray hair, wasted skin, and fat, muscular emaciation, even angina pectoris, sclerosis of the heart and arteries, and fibroid kidneys, with the height of a six-year-old child, with persistence of some of the milk teeth, thin cranium, absence of facial, axillary, and pubic hairs, and persistence of the thymus. In the case that came to autopsy, some of the organs showed an attempt at normal development in size. Some of the long bones had the delicate shafts of a child, the epiphyseal ends of youth, and the fusion of the real age.

Gilford thought at first of naming the condition micromegaly, on account of the contrast to acromegaly. The pituitary body was examined in one case and found negative, but, of course, without the application of such tests as are now required in the examination of that gland. Gilford discusses the various possibilities, and cites the views of others who have considered allied topics, such as dwarfism. It is hardly necessary to point out the differences between such processes as he describes in the bones, and the normal variations of development so carefully studied by Rotch.[1]

[1] *Transactions of the Association of American Physicians,* 1907. See also the useful article of E. Fuchs, "Vier Fälle von Myxœdem nebst Beiträgen zur Skiagraphischen Differentialdiagnose der verschiedenen Formen verzögerten Langenwachstums," *Archiv f. Kinderheilkunde,* 1905, xli, 60.

PART III.

DISEASES OF OBSCURE CAUSATION.

CHAPTER XX.

HODGKIN'S DISEASE.

By WARFIELD T. LONGCOPE, M.D.

Definition.—Hodgkin's disease is an affection characterized by painless progressive enlargement usually of several groups of lymph nodes and accompanied by a progressive anæmia. Often the spleen, and sometimes the liver, is enlarged.

Historical.—In 1832 a paper by Hodgkin, entitled "On Some Morbid Appearances of the Absorbent Glands and Spleen," appeared in the *Medico-Chirurgical Transactions*. Hodgkin described in this article a peculiar disease characterized by progressive enlargement of the lymph glands, associated with white deposits like suet in the spleen. There were seven cases in all, and among these were specimens which he had found in the Museum of Guy's Hospital. Strangely enough, most of these cases seem to have been examples of syphilis, tuberculosis, or possibly lymphatic leukæmia, so that in reality Hodgkin described only a few instances of the disease which now bears his name. Before this time reference had been made to a form of enlargement of the spleen in which white deposits were scattered through the pulp; and in association with this condition swelling of the lymph glands is mentioned. Bright[1] described briefly autopsies on several such cases, and Malpighi mentions probably the same condition in his *De Viscerum Structura*, published in 1669. To Hodgkin, however, is due the credit of having recognized a disease process.

In spite of the fact that Hodgkin's paper presented something quite new, the subject was virtually neglected for over twenty years. Markham,[2] it is true, in 1853, published details of a case which suggests the condition described by Hodgkin; but the disease was not generally recognized until 1856, when Wilks,[3] in England, and Bonfils,[4] in France, both reported cases resembling those of Hodgkin. Bonfils was ignorant of Hodgkin's work,

[1] *Essays on Abdominal Tumors*, New Sydenham Society, 1860, p. 148.
[2] *Pathological Transactions*, 1853, iv, 177.
[3] *Guy's Hospital Reports*, 1856, ii, 114.
[4] *Soc. Méd. d'Observat. de Paris*, 1856, i, 157.

and Wilks, too, did not realize, until after he had made his report, that the condition had been known before. In fact, unwittingly, he made use of some of Hodgkin's original specimens which had been preserved in Guy's Hospital Museum. Two years later Wunderlich[1] published an account of two cases with full histological descriptions, while reports of doubtful cases soon followed by Pavy[2] and Potain.[3] Finally, in 1865, Wilks[4] wrote upon the subject for a second time, brought together 15 cases, including the ones that Hodgkin had reported, and called the condition "Hodgkin's disease."

Sufficient had now been written to make the disease generally known. It was familiar to Virchow, among others, who gives a short account of the condition in his "Krankhafte Geschwülste," to Cohnheim,[5] Billroth,[6] and Trousseau.[7] But opinions differed so, during this early period, as to the true character of the disease, that in almost every important paper it is described under a different name. One need only mention such terms as "progressive multiple lymph gland hypertrophy" and "lymph adenoma" (Wunderlich), "lymphosarcoma" (Virchow), "malignant lymphoma" (Billroth), "pseudoleukæmia" (Cohnheim), "adénie" (Trousseau), and "desmoid carcinoma" (Schulz) to realize the chaotic condition of the older literature. Notwithstanding the fact that Hodgkin's disease was confounded with many other affections, it was separated very definitely by such writers as Trousseau, Wunderlich, Wilks, and a few others from leukæmia, tuberculosis, syphilis, and the malignant forms of lymphosarcoma. Virchow's work upon the diseases of the blood had been published many years before, and the absence of blood changes in Hodgkin's disease was often emphasized.

Wilks had placed some importance upon the attending anæmia and progressive cachexia, and wishing to distinguish the condition from lymphatic leukæmia, which was attracting much attention at that time, suggested as well as Hodgkin's disease the name "anæmia lymphatica." The prevalent opinion was that the disease was a variety of lymph gland tumor, often associated with enlargement of the spleen, and accompanied by progressive anæmia, fever, and cachexia.

The later history is involved principally in discussions upon the etiology and exact pathological histology of the growths. About 1885 a serious question arose as to the tuberculous nature of the disease, and this question has been debated to the present time. Certain observers, on the other hand, have concerned themselves with the relationship between Hodgkin's disease and lymphatic leukæmia, or have brought forward arguments for or against its classification as a true tumor. But recent studies in this country and Germany seem to have fixed a definite pathological basis for the classification of the disease. There are, however, certain authors who are not inclined to regard Hodgkin's disease as a pathological entity. They consider that there is a group of more or less distinct pathological conditions which together form a symptom complex. By some, certain forms of lympho-

[1] *Arch. f. Phys. Heilk.*, 1858, ii. 123.
[2] *Lancet*, 1859, ii, 213.
[3] *Bull. de Soc. d'Anat.*, 1861, vi, 217.
[4] *Guy's Hospital Reports*, 1865, xi, 56.
[5] *Virchow's Archiv*, 1865, xxxiii, 451.
[6] *Ibid.*, 1861, xxi, 439; 1862, xxiii, 479.
[7] *Clinique Méd. de l'Hôtel Dieu*, 1865.

sarcoma, simple hyperplastic conditions of the lymph nodes, and other forms of lymphoma, as well as the type of glandular enlargement described by Reed and others as Hodgkin's disease, should be included under one general heading. Warthin has found that only about one-third of his cases which were diagnosed as Hodgkin's disease have shown the pathological changes described by Reed and others. The majority of the other cases have presented pathological pictures of a condition which he terms lymphocytoma and describes as a hyperplastic or neoplasm-like enlargement of the lymph node dependent upon an overgrowth of the cells of the type of lymphocytes either of the small variety or of the large cells. He, however, considers that the alterations described by Reed and others represents a distinct condition.

That there exists a disease of the lymph nodes which in its pathological histology is characteristic is now well recognized by many authorities; and since many of the English writers as well as recent German and Italian writers are inclined to restrict the term Hodgkin's disease to this particular group of cases, it was thought best to consider the subject in this chapter from this point of view.

Etiology.—Distribution.—Hodgkin's disease seems to be pretty widely distributed over the countries of Europe and through America, and may exist in all parts of the globe, although, owing to the lack of reports from certain countries, this fact is difficult to ascertain. In this country the reported cases have occurred with few exceptions in whites. It is probably much more common than is generally supposed, for the writer has been able to collect 72 cases with fair clinical histories and full histological descriptions which have been reported since 1903. This does not include many cases reported, especially from Germany, in which the pathological changes alone are described. Including the cases of Diedrich and Fischer, reported before 1903, we have 86 cases from which to draw statistics. In Sternberg's series the clinical histories are not recorded. The disease is said to affect dogs, horses, and pigs (Friedberger and Fröhner,[1] Weil and Clerc,[2] Cadiot and Weil,[3] McFadyean,[4] and Hodgen[5]), but a more accurate and extensive study is necessary before one can assert that these glandular swellings in animals are the same as Hodgkin's disease in man.

Sex.—The disease is much more common in men than in women. Of the 100 cases which Gowers collected, 75 were in males, 25 in females; of the 102 cases which Fischer collected, 86 were in males, 38 in females; of Clarke's 43 cases, 32 were in males, 11 in females; and of the cases which the writer has collected, 58 were males and 28 females.

Age.—Young adults are especially susceptible, although the affection has been described in extreme youth and old age: 34 of Gowers' cases occurred between the ages of ten and thirty; 37 of Fischer's cases occurred between the ages of three and fourteen; 76 between the ages of fifteen and thirty-five, and only 11 after the thirty-sixth year. In the writer's series the cases occurred in the various decades as follows:

[1] *Veterinary Pathology*, Translation by M. H. Hayes, 1904.
[2] *Arch. de méd. Exp. et d'anat. Path.*, 1904, xvi, 462.
[3] *Ibid.*, 665.
[4] *Journal of Comparative Pathology*, 1903, xvi, 379.
[5] *Ibid.*, 382.

Years.	Cases.
Before 10	17
10 to 20	23
20 to 30	15
30 to 40	17
40 to 50	5
50 to 60	5
60 to 70	2
No age given	2
Total	86

Predisposing Causes.—Various factors have been suggested by different observers as predisposing causes, and of these the one most frequently mentioned is local inflammation. By certain authors a good deal of stress has been laid especially upon inflammations of the throat and also of the eyes, ears, and nose. Since the disease usually starts in the cervical lymph glands, it is natural that infection of the throat and tonsils should be looked upon with favor as a predisposing factor. Local irritation has been mentioned as a possible factor. Heredity is probably unimportant, and a history of syphilis can be obtained in comparatively few cases. There is no evidence to show that the disease can be transmitted from one person to another, although in a few instances a history of glandular swellings in other members of the family has been obtained (Warnecke).

The actual cause of Hodgkin's disease seems to be as obscure today as it was over seventy years ago. Although many factors have been brought forward as possible etiological agents, a satisfactory explanation to account for the origin of the disease is still wanting. The old idea that the process was a true tumor has to a large extent been relinquished. Unlike a neoplasm, the growth is usually encapsulated, does not, as a rule, invade the surrounding tissue, and produces no true metastases, since the secondary nodules are believed generally to arise from preëxisting lymphoid tissue. The fact, too, that the growth involves secondarily only one type of structure, namely, lymphadenoid tissue, has been used as an argument to differentiate it from the true tumor metastases. Nevertheless, certain recent investigators are inclined to believe that the condition may be very nearly related to the true tumors. It is unquestionable that the tumor masses may at times be non-encapsulated and may extend into the surrounding tissues. Yamasaki has reported two cases in which he considered that the disease terminated in sarcoma. Gibbons,[1] from a study of nine cases, considers that the capsule is infiltrated in most cases, that the growth extends beyond the capsule in many, and infiltrates the surrounding tissues occasionally. He therefore classes Hodgkin's disease with malignant tumors.

Bacteriological Studies.—Many investigators are of the opinion, nevertheless, that the changes in the lymph nodes show a close resemblance to a chronic inflammatory process. Bacteriological findings, however, have given most unsatisfactory results. Pyogenic cocci and a number of unidentified organisms have been isolated by several observers,[2] from the blood of patients suffering from this disease, and from the glandular swellings

[1] *American Journal of the Medical Sciences*, 1906, cxxxii, 692.

[2] Verdelli, *Cent. f. inner. Med.*, 1895, xvi, 24; Brigidi d. Piccoli, *Ziegler's Beiträge*, 1894, xvi, 388; Delbet, *Compt.-rend. de l'Acad. des Sciences*, 1895, No. 24.

both before and after death; but the results have not been uniform, and the work remains unconfirmed. Contradicting these findings, most observers have obtained no growth of bacteria from the blood or grandular tumors. Thus, Fischer[1] in 12 cases found blood cultures and cultures from the extirpated glands sterile.

Experimental Inoculations.—Delbet claims to have produced lymphomatous nodules experimentally in animals by inoculations of a microörganism isolated from a case of Hodgkin's disease. Recently, Cignozzi,[2] by inoculating into animals pieces of gland from a case of tuberculosis simulating Hodgkin's disease, claims to have produced an enlargement of the lymph glands which microscopically presented the same appearance as the glands removed from the patient. Although tubercle bacilli were found in the enlarged glands, there were no histological tubercles.

Emulsions of glands from three of the Pennsylvania Hospital series of cases have been inoculated subcutaneously into small monkeys, and in one case glands were fed to those animals. One monkey has been under observation for a year. Several weeks after the inoculations the monkeys showed transitory general glandular enlargement, but microscopically the enlarged axillary gland showed only a simple hyperplasia.

Tuberculosis.—The one etiological possibility which has been most seriously considered is tuberculosis. The development of this view goes back many years, and recently the subject has been repeatedly discussed. In 1884 Weigert described a case of pseudoleukæmia, sections from the glands of which showed tubercle bacilli. Previously, in 1874, Hilton Fagge[3] had described a case of primary glandular tuberculosis simulating Hodgkin's disease, and in 1887 another instance was recorded by Delafield.[4] Similar observations were reported by Weishaupt,[5] Askanazy,[6] Cordua,[7] and others. The idea of the association of the two diseases became more and more prevalent, until finally, in 1898, Sternberg's[8] paper appeared. This author brought forward the view that pseudoleukæmia was a peculiar form of tuberculosis. To substantiate his assertion, he reported a number of cases of pseudoleukæmia in the organs or in the glandular swellings of which he could demonstrate either tuberculosis or tubercle bacilli. Of the 15 cases which he described, 13 were considered as pseudoleukæmia; 8 showed tuberculosis of one or more organs or tubercle bacilli in the glandular swellings. Before this work it had already been recognized by Weishaupt,[9] Westphal, Diedrich,[10] and Fischer that tuberculosis might appear as a secondary infection in Hodgkin's disease, but these authors considered that the two diseases were distinct processes, and assumed no etiological importance for the tubercle bacillus. Sternberg's results have been widely discussed, his views followed by some, but opposed or modified by many.

Evidence is certainly accumulating to show that it is impossible to demon-

[1] *Arch. f. klin. Chir.*, 1897, lv, 467.
[2] *Riforma Medica*, 1906, xxii, 875.
[3] *Pathological Transactions*, 1874, xxv, 235.
[4] *Medical Record*, 1887, i, 424.
[5] *Pseudoleukämia und Tuberculosis, Inaug. Diss. Tübingen*, 1891.
[6] *Ziegler's Beiträge*, 1888, iii, 411.
[7] *Arb. a. d. Path. Inst. in Göttingen*, 1893, p. 152.
[8] *Cent. f. d. Grenzgebiete d. Med. und Chir.*, 1899, ii, 641, 711, 770, 813, 847; *Zeit. f. Heilk.*, 1898, xix, 21.
[9] *Deut. Arch. f. klin. Med.*, 1893, li, 83.
[10] *Beit. zur klin. Chir.*, 1896, xvi, 376.

strate tuberculosis or tubercle bacilli in the glands in a large majority of the cases of Hodgkin's disease. Fischer, in his 12 cases, could not demonstrate tubercle bacilli in sections from the glandular tumors in any one, while inoculations of portions of the lymph nodes into animals was attended with negative results. Of Reed's[1] 8 cases, 1 died of miliary tuberculosis. No tuberculosis could be found in two other autopsies. In the 5 operative cases nothing suggesting tuberculosis could be found in the lymph nodes, nor could tubercle bacilli be demonstrated. In two instances inoculation experiments were negative. In none of the writer's[2] series of 8 cases, 4 of which came to autopsy, was there any evidence of tuberculosis. Inoculation of portions of the lymph glands into animals from 4 different cases gave negative results. Similarly negative results were obtained by Simmons[3] from inoculation of portions of the glands from 5 of a series of 9 cases into animals. Yamasaki,[4] in a study of 6 autopsies on fatal cases of Hodgkin's disease, found old, small foci of tuberculosis in the bronchial lymph nodes, apices of the lungs, or tuberculous ulcers of the intestines or tuberculosis of the spleen in 4 instances. One inoculation from portions of the lymph nodes produced tuberculosis in animals; twice the inoculations gave negative results. Benda[5] reports a study of 9 cases. Acid-fast bacilli were found in the glands from one case which he states positively were not tubercle bacilli. Only a few of his cases were associated with tuberculosis, and he concludes that pseudoleukæmia and tuberculosis are distinct processes, to be differentiated even when they occur together in the same gland. Aschoff[6] reports 5 cases, in all of which inoculations of portions of the glands into animals produced no results. Warnecke,[7] in one of 9 cases studied by him, found apical tuberculosis. From 4 cases inoculation experiments gave negative results. These authors conclude that tuberculosis has no etiological significance in the production of Hodgkin's disease. The two diseases may be associated, but tuberculosis appears only as a secondary infection. Sternberg,[8] himself, has recently modified his statement as to the character of the disease, and although he considers that the tubercle bacillus may have something to do with the lesions in certain instances, he admits that it is not the only cause, and considers the condition as a granuloma. The idea that the disease is allied to the infectious granulomas is a view concurred in by many.

Recently White and Proescher[9] have described spirochætes which they have found not only in the glands from cases of Hodgkin's disease, but of lymphatic leukæmia and lymphosarcoma. The structures which they described could be readily stained in sections by the Levaditi method, and sometimes were observed in enormous numbers. It remains yet for these observations to be confirmed.

Pathology.—Lymph Glands.—The anatomical picture which this disease presents at autopsy is often one of a striking character. If the glandular

[1] *Johns Hopkins Hospital Reports*, 1902, x, 133.
[2] *Bull. Ayer Clin. Laboratory of Penna. Hosp.*, 1904, No. 1, p. 4.
[3] *Journal of Medical Research*, 1903, ix, 378.
[4] *Zeit. f. Heilk.*, 1904, xxv, 267.
[5] *Verhand. der. Deut. Path. Gesellschaft*, 1904, Heft 1, p. 123. [6] *Ibid.*, p. 129.
[7] *Mitth. aus d. Grenzgebiete d. Med. und Chir.*, 1904, xiv, 275.
[8] *Verhand. der Deut. Path. Gesellschaft*, 1904, Heft 1, p. 129; *Erg. d. allg. Path. und path. Anat., Lubarsch-Ostertag*, 1905, 9th Jarhgang, p. 502.
[9] *Journal of the American Medical Association*, 1907, xlix, 115, 1988.

PLATE V



Hodgkin's Disease. Cervical, mediastinal, axillary, bronchial, and retroperitoneal lymph nodes.

involvement is widespread, great collections of tumors are seen in the neck, thorax, axillæ, retroperitoneum, mesentery, and inguinal regions. But wherever the tumors are found, whether they are generalized or confined to one situation, such as the neck or mediastinum, their general appearance is much the same. When the lobulated tumor masses are examined carefully one sees that they are composed of separate nodules, varying greatly in size, the larger nodules usually forming the central portion of the masses, while smaller tumors are attached to the superficial regions. In typical instances the nodes are oval or round, often somewhat irregular, but still presenting a smooth surface; they are not fused, but are discrete and separate, even in the largest masses, for the single tumors are only held together by loose connective tissue. Often by rapid dissection these large, conglomerate tumors may be resolved into single smooth nodes. The color is white, pinkish, semitranslucent gray, or a delicate cream tint.

The nodes vary a great deal in consistency, and, indeed, it has been common since Virchow's description of the condition to distinguish between the hard and soft forms of lymphoma. This distinction is, however, more or less artificial, for the hardness or softness of the nodes depends upon the progressive changes which have taken place in the tumors themselves. In certain cases all the glands may be soft, some giving a distinctly elastic sensation on palpation, others almost suggesting the presence of fluid, so near is the feeling to one of fluctuation; while, again, all the tumors may be firm or extremely hard. Occasionally, in a single group of tumors some are soft, some elastic, some firm, and others again seem almost to fluctuate. Usually the smallest or youngest nodes are soft, while the larger ones are firm; but the reverse may be true, and the size of the tumor may be no index to its consistency (Plate V).

The cut section is often very characteristic. The surface of the softer glands is pinkish gray, semitranslucent, rather juicy, and either bulging or slightly lobulated. The latter appearance is more pronounced in the larger tumors. The irregular character is produced by depressed bands of yellowish tissue which sometimes extend from the capsule toward the centre of the mass, sometimes cut up the surface irregularly, but in any event leave bulging areas of semitranslucent gray tissue between them. In the firmer nodes the yellowish bands are thick, numerous, and predominate, while the very hardest nodes may be entirely composed of this yellowish or white, somewhat opaque tissue. Rarely small, opaque gray or yellow foci of softening are scattered over the cut surface.

Although in the majority of instances the tumors present the appearance just described, their character may be altered by certain influences. The discrete nature of the single tumors has always been emphasized in the descriptions, but as Ribbert[1] and Benda[2] state, and Yamasaki[3] and Diedrich[4] have described, the growths at times appear to extend through the capsule into surrounding tissues in much the same way as a new-growth. It must be noted, nevertheless, that the tumors extend in bulk, having a regular margin along the line of advancement compressing the surrounding tissue, and thus forming

[1] *Die Geschwulst Lehre*, 1904, p. 235.
[2] *Verhandlung der Deut. Path. Gesellschaft*, 1904, Heft 1, p. 123.
[3] *Zeit. f. Heilkunde*, 1904, xxv, p. 267.
[4] *Deut. med. Wochen*, 1908, xxxiv, No. 27.

a false capsule. They do not infiltrate in an irregular manner. In the series of autopsies at the Pennsylvania Hospital a very rapidly fatal case which exemplifies this type of growth was studied. The lower portion of the neck and supraclavicular regions were filled with tumors which extended into the muscles and involved the thyroid gland.

If the nodes become secondarily infected, they may be found matted together, firmly adherent, and surrounded by inflammatory tissue. The same condition is often noted after prolonged treatment by the *x*-rays. In old tumors bright yellow areas of fatty degeneration may be seen. In rare instances cone-shaped hemorrhagic areas may be seen at the periphery of the gland, the base of the cone lying beneath the capsule. This condition has been noted twice at the Pennsylvania Hospital, Philadelphia. The centre of the area is necrotic, the periphery composed of a hemorrhagic area.

The histology of the lymphomatous nodules, formerly so imperfectly understood, has recently received very careful study, and the results obtained from these modern investigations leave no doubt that the microscopic changes are specific and characteristic for this disease. The account given by Ribbert in *Die Geschwulst Lehre* is excellent. The descriptions of Diedrich,[1] Fischer,[2] Reed,[3] Simmons,[4] Longcope,[5] Yamasaki,[6] Benda, and many others all agree in establishing a very definite microscopic anatomy for the condition.

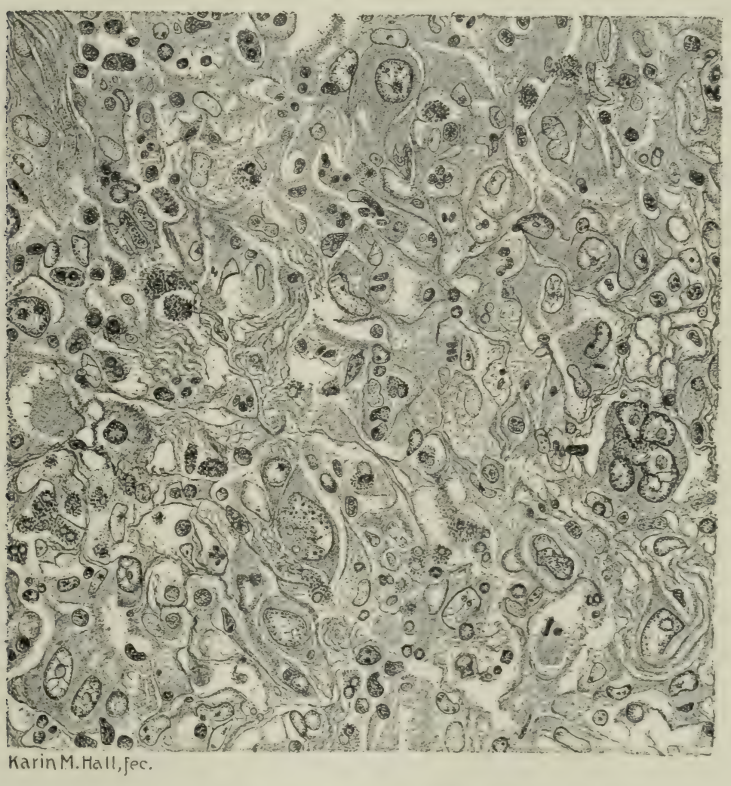
The first well-marked microscopic changes are seen in the smallest glands or often in the nodes immediately adjacent to the main tumor masses. They consist in a hyperplasia of the lymphoid cells with active proliferation at the germinal centres of the lymphoid follicles. There is besides increased vascularity and beginning proliferation of the reticular endothelium. Benda likens the changes to an early inflammatory process. The normal structure of the node is fairly well preserved. The lymph sinuses are dilated, and contain small and large lymphocytes and polymorphonuclear leukocytes, along with which eosinophiles are frequently seen, and endothelial cells. In the endothelial cells covering the reticulum of the node karoykinetic figures may usually be found, and are often numerous. The reticulum itself is prominent. Although the lymphoid cell predominates in the follicles and lymph cords, still one may see many other types of cells mixed in with them and in greater numbers than occurs normally. Large lymphocytes, epithelioid cells, plasma cells, mast cells, and eosinophilic leukocytes are often distributed quite plentifully.

As the process grows slightly older, the proliferation of cells increases and the thickening of the reticulum becomes more noticeable, until at quite an early date almost all traces of the normal structures are lost. Only here and there can be seen indefinite remains of the lymphoid follicles, centred, perhaps, by a germinal centre; or a few spaces representing what is left of the lymph sinuses. At this period sections have quite a uniform appearance. The node is surrounded by a definite capsule often somewhat thickened but distinct. Throughout the node there is a reticulum forming a meshwork of varying coarseness, which encloses cells of different types; while narrow

[1] *Beiträge zur klin. Chir.*, 1896, xvi, 376.
[2] *Arch. f. klin. Chir.*, 1893, li, 83.
[3] *Loc. cit.*
[4] *Journal of Medical Research*, 1903, ix, 378.
[5] *Loc. cit.*
[6] *Loc. cit.*

bands of young connective tissue usually divide the glands into irregular lobules. Lying in the meshes of the network one sees small and large lymphocytes, plasma cells, polymorphonuclear leukocytes, eosinophiles, epithelioid cells, and uninuclear and multinuclear giant cells. These various elements are not arranged to form any definite structures, but simply fill in the spaces of the reticulum to make one solid whole. The various cell types are not, however, equally distributed through the glands. Whereas, in some portions lymphoid cells predominate, suggesting the remains of

FIG. 4



Hodgkin's disease. Lymph node, high power drawing.

ancient follicles, in other parts epithelioid cells, giant cells, or even eosinophiles, may be the prevailing elements. The tumor at this stage represents the soft type of lymphoma (Fig. 4).

In intermediate periods the multinucleated giant cells are often one of the most constant and striking features. They were noted by Virchow in his specimens, and later, in 1872, Langhans speaks of the same structures. As suggested by Reed and others they are probably derived from the uninuclear giant cells, which in turn take their origin from the reticular endothelium.

The uninuclear giant cell is very irregular in form and has a clear protoplasm containing one or several pale nuclei, which often take on the most bizarre shapes. Outlining the nucleus is a fine, deeply staining vein of chromatin, and in the centre a well-defined chromatin network with one or several deeply staining and sharply defined nucleoli. The multinucleated cell is a further development of the uninuclear variety where the nucleus has undergone either direct or indirect division. In the larger multinucleated giant cells, which are sometimes of astonishing size, the nuclei, often four to ten in number. are heaped together in the periphery or centre of the cell, and their general pallor, contrasting with the deeply colored definite chromatin network and prominent nucleoli, with their very irregular forms, gives the cells a most characteristic appearance. A second form of giant cell is sometimes seen. This one differs from the first in that the nuclei stain deeply and are arranged in the shape of a horseshoe about the periphery of the cells. These cells resemble very closely the Langhans giant cells of tuberculosis.

Occasionally the proliferation of the endothelioid cells is so extensive that they form large masses and solid columns, filling the lymph sinuses, and since the cell outline is indistinct, these cords of cells may give the appearance of mases of protoplasm containing many nuclei. Among others, Weishaupt[1] has called attention to these structures.

Together with the extensive cellular proliferation, cellular degeneration is also to be noted. Nuclear fragments are scattered through portions of the glands, and not infrequently areas of necrosis are found. These may be sufficiently large to be seen macroscopically when they appear as small, yellow areas. They are infiltrated with fibrin and usually surrounded by moderate numbers of leukocytes. The cells may also undergo fatty degeneration as was pointed out by Benda and others.

As the disease progresses the connective tissue increases. Coarse, fibrous bands run from the capsule into the tumor, cutting it into lobules, and the reticulum thickens and becomes more prominent, thus narrowing the cellular spaces of the mesh (Fig. 5 and Plate VI). Occasionally it undergoes hyaline degeneration. In still later stages the tumors are composed principally of fibrous tissue varying in cellular contents. The cellular part of the tumor is restricted to small islands lying between the coarse, connective-tissue bands. Sometimes there may be many giant cells often very large in size. Finally, these cellular islands are replaced entirely or in part by connective tissue, and only here and there small collections are left to remind one of the former structure so rich in different varieties of cells.

It may be seen that while in the early stages the structures are very cellular, in the later stages the nodes are almost completely converted into fibrous tissue, and without studying the development of the process the first and last stages might almost be mistaken for different conditions. It has been pointed out that this sequence of events does not march regularly through all the groups of enlarged nodes. Some, even large ones, may be quite cellular and soft, while other smaller tumors are hard and show much new connective-tissue formation. Neither do single nodes always show the same stage of development throughout, for parts may be quite cellular, while the remainder is composed principally of fibrous tissue.

[1] *Arb. aus dem Gebiete der Path. Anat. u. Bact. aus dem. Path. Anat. Inst. z. Tübingen,* 1891–92, i, 194.

PLATE VI

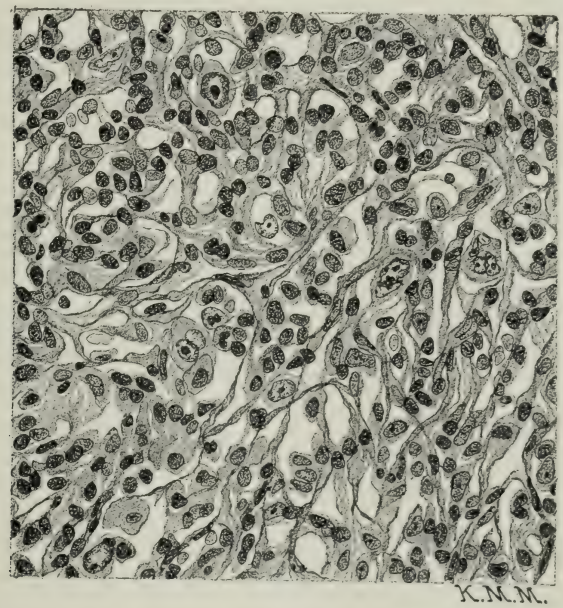


Lymph Node, showing increase of reticulum.

Mallory's connective-tissue stain.

Aside from the progressive increase in the size of the nodes, there is usually an increase in numbers. The recent work of Sabin,[1] upon the development of the lymph nodes, has thrown some light upon the regenerative process of lymph nodes in pathological conditions. Although Meyer[2] has not been able to determine that after resection there is any physiological recurrence of lymph glands in the mesentery or inguinal region of dogs, others have observed a regeneration of glands in pathological conditions. Ritter has found a new formation of axillary glands in axillæ which were the seat of lymphatic metastases following primary carcinoma of the breast. As the preëxisting nodes are rendered functionless in Hodgkin's disease, it is probable that an attempt is made on the part of the tissues to produce new glands. This

FIG. 5



Hodgkin's disease. Lymph node, showing increase of reticulum.

regenerative process starts in small masses of lymphoid cells which, as Ribbert believes, are to be regarded as the anlage of the lymph glands and are to be found in the connective tissue surrounding the tumor masses. As they develop, these embryonic organs become involved in the general lymphatic disturbance, and instead of pursuing their normal growth are transformed into lymphomatous nodules and continue as such.

It has already been stated that the general character of the growth, the thickened reticular mesh enclosing lymphoid cells, epithelioid cells, plasma cells, giant cells, and eosinophilic leukocytes, forms a picture so characteristic

[1] *American Journal of Anatomy*, 1905, iii, 184; iv, 355.
[2] *Johns Hopkins Hospital Bulletin*, 1906, xvii, 185.

that according to recent writers it cannot be mistaken for any other condition. Among the cell types the eosinophiles have been emphasized as particularly characteristic. These cells may be either polymorphonuclear, showing two or more lobes, or uninuclear. The former variety is most common, but the latter may also occur in comparatively large numbers. The eosinophiles are frequently abundant and are rarely absent in any case. Their presence was first noted by Goldman,[1] and since then many other investigators have called attention to their occurrence. Reed, in particular, finding them in a large proportion of her cases, lays special stress upon their presence as assisting in the diagnosis of the affection. Although small numbers of eosinophilic leukocytes have been seen, especially by Howard and Perkins,[2] in lymph nodes which were the seat of tuberculosis, sarcoma, and metastatic carcinoma, they rarely attract particular attention. It is true that a profusion of eosinophilic leukocytes has been observed by Councilman, Mallory, and Pearce[3] in the lymph nodes from fatal cases of diphtheria, and by Pearce[4] in the same situations in scarlet fever. Except for a few such conditions, Hodgkin's disease seems to be one of the only pathological conditions affecting lymph nodes in which the acidophilic cells play such an important role.

Their origin has been much discussed. Goldman considered that they were attracted to the nodes from the circulating blood, while other authors consider that the cells are formed in situ either from preëxisting eosinophilic cells or by the development of acidophilic granules in the protoplasm of hyaline leukocytes (Howard and Perkins). The exact relation of these cells to the pathological process and their significance has not as yet been determined.

Secondary Growths.—The lymph nodes must be considered as the most important seat of the disease, but the other organs of the body are not exempt, for secondary deposits may occur in many different situations. It was first thought that these secondary growths were of a true metastatic nature, but it is now usually believed that they are not true metastases, but growths arising from the lymphoid tissues of the organ in which they are situated. Contrary to the idea expressed by Borst,[5] Lubarsch,[6] Fischer, Benda, Reed, and others, Ribbert holds the older view, and considers that the cells from a lymphomatous nodule either grow along the lymphatics or are transported by the lymphatics from diseased lymph nodes to healthy ones.

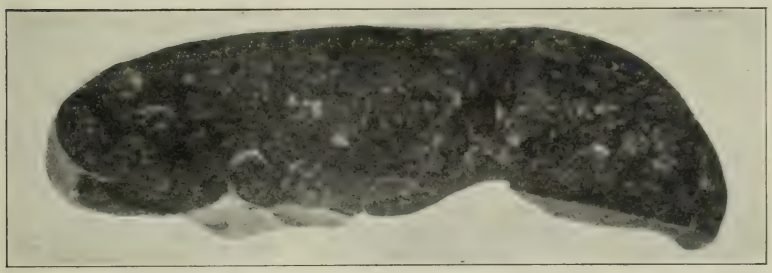
Spleen.—If the spleen is the seat of secondary growths, it is often enlarged, but rarely to a very great size, although in unusual cases, as one in the writer's series, the organ weighed 1850 grams. It is usually regular, preserving the normal contour, and is firm. The capsule may be covered with fibrous adhesions. Sometimes the surface is slightly nodular owing to the protrusion of the lymphomatous nodules beneath the capsule. The organ usually presents a mottled or marbled appearance, which is much more marked on section, and is red, purple, and grayish white. When the secondary deposits are numerous, the red pulp is streaked and mottled with irregular pearly-

[1] *Cent. f. allg. Path. u. path. Anat.*, 1892, p. 665.
[2] *Johns Hopkins Hospital Reports*, 1902, x, 249.
[3] *Journal of Boston Society of Medical Sciences*, 1900, v, 295.
[4] *Medical and Surgical Reports of Boston City Hospital*, 1899, tenth series, p. 22.
[5] *Die Lehre von den Geschwülsten*, 1902, p. 480.
[6] *Virchow's Archiv*, 1906, clxxxiv, 213.

white or yellowish lines and masses varying in size, according to the extent of the process. The cut surface is compared by many to red porphyry. On close inspection it will be seen that the smaller and younger growths follow rather closely the lines of the trabeculæ, and the smallest masses are rarely to be distinguished from the Malpighian bodies, which are usually enlarged. Of course, if the process is but slightly advanced, only a few small, scattered, semitranslucent, grayish areas may be seen, and the spleen may be very slightly, if at all, enlarged. Besides the typical tumor growths, there may also be infarctions along the margins of the organ (Fig. 6).

Microscopically, the gray or whitish nodules appear in structure exactly like the lymph nodes. The youngest growths are always found in the Malpighian bodies (Benda and Ribbert). As they become older and larger this relationship can no longer be traced. There may be much new connective-tissue formation and many foci of necrosis. The margins are usually well defined and the pulp spaces about the advancing edge are often flattened out, forming an apparent capsule. The growths, pushing their way, may extend into the bloodvessels (Fig. 7).

FIG. 6



Hodgkin's disease. Spleen.

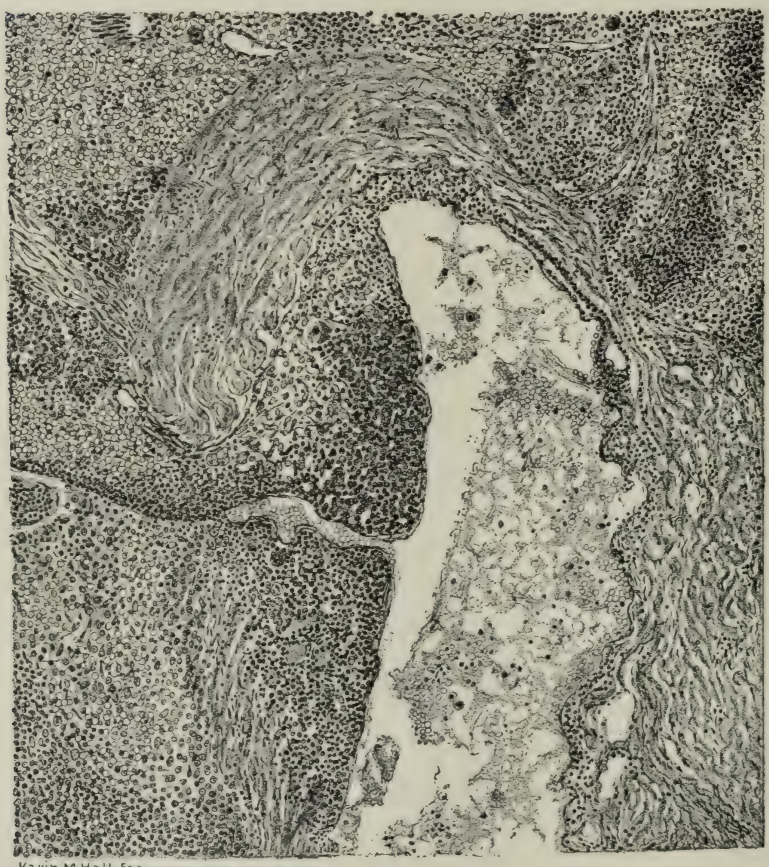
Liver.—The liver may be enlarged, but it is not nearly so often increased in size as the spleen. Besides the secondary deposits, which are occasionally seen and are scattered over the surface in the portal areas as pearly white masses of various size, there may be fatty degeneration or a slight perilobular cirrhosis. The secondary deposits usually arise in the lymphoid tissue of the portal spaces and pursue much the same course as the growths in the spleen.

Other Organs.—More rarely lymphomatous nodules are found in the kidney, which, except for this lesion, shows no other changes characteristic of the disease. Occasionally the lungs are extensively involved with secondary growths. Here, as in the other organs, the growths have the same general appearance and microscopic structure as is seen in the lymph nodes. The youngest nodules are found about the bronchi, and start their growth in the masses of lymphoid cells scattered through the lungs in these situations. Indeed, as Fischer has stated, practically any organ or even tissue of the body, if it contains lymphoid tissue normally, may be the seat of secondary lymphomas. Growths have been described in the pericardium, pleura, thymus (where Ribbert states that the tumor may start), tonsils, bone

marrow, skin (Crosz), and intestinal tract. Wells and Weaver[1] have described cases of the latter condition as pseudoleukæmia intestinalis.

In the bone marrow true growths occur not infrequently (Benda), but undoubtedly, as Pinkus points out, many of the cases formerly called myelogenous pseudoleukæmia are, in fact, instances of multiple myeloma. Besides the secondary growths, such alterations in the blood-forming cells as an increase of lymphocytes (Gutig) and increase of eosinophilic myelocytes has been noted.

FIG. 7



Hodgkin's disease. Growth of lymphomatous nodule into vein of the spleen.

A condition which by some has been thought to have a possible connection with Hodgkin's disease is the growth of lymphomatous tumors which occurs in the parotid and lacrimal glands. First described by von Mikulicz, the

[1] *American Journal of the Medical Sciences*, 1904, cxxviii, 837.

disease has been studied subsequently by several investigators, and recently Minelli[1] has collected 30 reported cases and added one of his own to the literature. According to Minelli the growth starts in small deposits of lymphoid tissue, which are found under normal conditions in this gland, and as the tumor increases in size it destroys by pressure the surrounding acini of the parotid gland. The histological picture is not unlike that described for Hodgkin's disease, although it may be altogether a different process. In Minelli's cases there were great numbers of eosinophiles. Of the 30 cases, two were followed by general enlargement of the lymphatic glands.

Symptoms.—Onset.—The first symptom to attract attention in the great majority of cases is swelling of the superficial lymph glands; and not only is it the first manifestation, but often, in the early part of the affection, the only one which disturbs the patient. For during what may be called the first stage of the disease there is no anæmia, no loss of weight, and no general ill health, so that the patient may come in good physical condition to ask advice about the tumor masses which inconvenience him or are disfiguring. If, however, the deep glands instead of the superficial glands are primarily involved, the onset is more insidious. Occasionally there is a history of malaise or attacks of fever. Rarely the disease progresses silently until what may be termed the second stage is reached, when symptoms referable to pressure exerted by the deep glands upon the surrounding structures make their appearance. Dyspnœa, as in one of Simmonds' cases, jaundice (Simmonds and Warnecke), pain in the arms (Hitschmann and Stross[2]), œdema of the legs and abdomen (Yamasaki), and violent abdominal pain (Brooks[3]) may be the first outward and visible sign of the disease. But such cases are very exceptional.

Swelling of the superficial lymph glands occurred as the first symptom in 52 out of 78 of Gowers' collected cases, and in 71 of the 86 cases tabulated by the writer. The favorite situation for the glands to make their appearance is in the cervical region. Thus, in Gowers' 78 cases primary enlargement of the glands of the neck was noted 36 times, and in the present series 57 times. The order of frequency in which the other groups are affected first is given by Gowers as follows: (1) Axillary, (2) inguinal, (3) bronchial, (4) mediastinal, and (5) retroperitoneal. As accurately as can be told from the histories, the axillary glands were the first to enlarge in 4 cases of this series, the retroperitoneal in 4, the mediastinal in 2, the inguinal and the epitrochlear in one each.

Glandular Swelling.—In the cervical region the disease seems to have a predilection for the nodes situated in the posterior triangle, and although the submental and submaxillary groups may be involved either early or late, it is more usual to find the tumors above the clavicles or in the postauricular region. Usually the disease starts in one side of the neck, and there seems to be no preference for either side, since the right and the left are affected about equally. The swelling may be entirely confined to the right or the left side, or may spread rapidly or only after a period of months or years to the opposite side. The glands may swell on both sides at the same time.

Having once made its appearance, the rapidity with which the disease

[1] *Virchow's Archiv*, 1906, clxxxv, 117.
[2] *Deut. med. Woch.*, 1903, No. 21, p. 364.
[3] *Proceedings of the New York Medical Society*, 1903.

progresses is somewhat variable. Clarke, Dreschfeld,[1] and others have recognized two types, the acute and chronic. In the first variety one group of glands after another becomes enlarged until all the superficial and deep glands are swollen to an enormous size. The progress usually takes place in an orderly manner, the disease spreading from one group of nodes to its neighbor, so that there may be a descent down the cervical chain to the supraclavicular, the axillary and mediastinal; or an ascent from the inguinal nodes along the pelvic chain of lymphatics to the retroperitoneal glands. In the more chronic cases the disease, although progressive, is slow in its march, and stops for months or longer with the enlargement of a single group of glands. But sometimes, after months of quiescence, the disease, as Trousseau has said, fairly bursts into activity and spreads with great rapidity. Finally, there is a group of cases in which the swelling is confined throughout the disease to two or three groups of lymph nodes, or even to a single group. In such instances the development of the tumors is usually slow, and unless accidents happen the affection may be prolonged over several years. At any time, however, a general eruption of tumor masses may take place. It is said that, of themselves, single glands may vary in size from time to time.

The superficial swellings are painless, and unless they become the seat of a secondary infection they are not tender to touch. The tumors can readily be mapped out beneath the skin, and when they have not attained a great size can be freely moved about and felt as discrete, oval, round, or slightly irregular masses of various sizes. Often they are moderately soft and elastic, sometimes almost giving the sensation of fluctuation; but in other cases they are quite firm or even of an extreme hardness. When the tumors are very large it is more difficult to move them about, for they are packed closely together and the skin is stretched tightly over them. But even in the largest tumors, which may feel like solid lobulated masses, one can find glands about the margins, which are regular and freely movable. The tumors are never adherent or matted together except from some secondary cause. After prolonged *x*-ray treatment the nodes may be densely matted together and adherent to the surrounding tissues. They do not soften, break down, or ulcerate through the skin. Over the very large masses the skin may be stretched and taut, so that it is smooth and shiny, but it is not reddened or inflamed.

As the disease advances and the tumor masses grow in size, a series of pressure symptoms usually develops, which are varied in their nature and depend naturally upon the situation of the enlarged glands. This may be considered as the second stage of the disease. With the enlargement of the cervical nodes the trachea may be compressed, giving rise to cough and varying degrees of dyspnœa. The latter symptom is unfortunately only too common, and of all, perhaps the most horrible. Sitting up in bed, with great deforming tumor masses bulging from the sides of his neck, and limiting the motion of his head, the patient, drooling saliva, his mouth open like a fish, gasps for breath. Very slowly, but very surely, the dyspnœa increases, until he dies, strangling. Trousseau has given the most graphic description of the difficulty in performing tracheotomy under these circumstances (Plates VII and VIII).

Occasionally the larynx and trachea are pushed far to one side. There

[1] *Brit. Med. Jour.*, 1892, i, 893.

PLATE VII



Hodgkin's Disease.

PLATE VIII



Hodgkin's Disease.

may be paralysis of one or both recurrent laryngeal nerves. Pressure upon the vessels of the neck gives rise to cyanosis and œdema of the face. One of the jugular veins may become thrombosed. In certain instances there is a fair degree of exophthalmos. Paralysis and marked swelling of the left side of the tongue occurred in one instance. Besides this there was difficulty in deglutition, pain on the left side of the face, and paralysis of the sixth nerve on the left side. If the tumors involve the tonsils and posterior pharynx, which occasionally happens, the patients are forced to breathe through the mouth, which they hold open. Deafness may develop. Dysphagia is not at all uncommon.

Masses in the mediastinum may cause dyspnœa, cough, and dysphagia, or if they press upon the pericardium they may impede the heart's action. Pressure upon the great vessels causes dilatation of the veins or œdema of the upper extremities; while pressure from enlarged axillary glands upon the vessels and nerves may give rise to swelling of the hands and arms, or pain in the arms. With enlargement of the bronchial and mediastinal glands, effusion into the pleural sacs occurs in a certain number of instances. This is usually seen only late in the disease. The fluid is most often serous, although chylous effusions are mentioned. Edsall[1] has described in one case a curious type of milky, albuminous effusion into the pleura which at first sight appeared to be chylous in character. A very marked emphysema may develop.

In the abdomen, groups of enlarged nodes may bring about various complications. Jaundice not infrequently develops as a result of the pressure by gastrohepatic glands upon the bile ducts; and mild symptoms of pyloric obstruction may accompany the swelling of glands about the pylorus. Pain, simulating that in appendicitis, may accompany swelling of the mesenteric nodes (Brooks). Following pressure by enlarged retroperitoneal, iliac, and inguinal masses, violent and persistent pains in the legs or œdema of the lower extremities may develop. Ascites is not uncommon, and there may be anasarca.

Secondary Growths.—Besides the disturbances caused by enlargement of the glands themselves, symptoms may arise from the growth of secondary masses in the various organs. When tumor masses make their appearance in the lung, there may be cough and some expectoration. Unless they are very massive the pulmonary growths cannot always be detected, although areas of dulness, combined with harsh breathing and rales, may raise suspicion of their presence. Definite circulatory disturbances are rare.

Violent gastro-intestinal symptoms may result from the development of a growth in the lymphoid tissues of the wall of the stomach or intestines. Wells and Weaver have described such a case in which the wall of the stomach alone weighed 1300 grams. In but 34 of 238 autopsies upon cases of Hodgkin's disease collected from the literature have they found mention made of intestinal involvement. The condition is to be distinguished in its etiology and pathological anatomy from lymphosarcoma and tuberculosis. It may be mistaken during life for carcinoma or tuberculosis.

In the majority of cases the spleen is palpable and often greatly enlarged, although it seldom reaches the size which it attains in leukæmia. An involvement of the spleen was present in 34 of 58 cases in which the condition of

[1] *New York Medical Journal*, 1905, lxxxii, 838, 901.

this organ was noted. The enlargement depends principally upon the number and size of the secondary growths in that organ. It is exceedingly rare for the nodules to be sufficiently prominent to be felt through the abdominal wall. The liver is increased in size in a smaller proportion of cases. It was the seat of secondary deposits in 26 of 52 cases. The enlargement may be due to the secondary deposits, but perhaps is more commonly caused by a fatty degeneration which occurs not infrequently in this disease. The kidneys attract little or no attention. There is nothing characteristic in the urinary secretion, and if secondary growths do occur in this organ their presence may and usually is only determined at autopsy.

Skin Changes.—Much interest is attached to the cutaneous changes which may arise during the course of the disease. Aside from the pigmentation which may follow the use of arsenic, a brownish discoloration or mottling which is usually associated with enlargement of the retroperitoneal lymph nodes is seen occasionally. The origin of this pigmentation has been ascribed by some observers to pressure upon the cœliac plexus by tumor masses. Pruritus is an exceedingly annoying symptom, which may be met with in some cases. It may be persistent and severe. This symptom was noted in three of the writer's collected cases.

Secondary growths may occur directly beneath the skin in unusual regions. They are seen at times about the breasts, in the back, or in the abdominal wall. Lying under the skin, they form hard masses of various sizes. Grosz[1] has recently described a most interesting and curious skin condition which he terms lymphomatosis cutis. The patient had large lymphomatous tumors in the neck and axilla. The blood changes were unimportant. The leukocytes varied from 12,000 to 18,000, and there was no increase in the lymphocytes. Throughout the skin on the right side of the chest there were great numbers of tumors varying from the size of a lentil to the size of a walnut. The smallest ones were round, soft, of a brownish red color, and slightly sensitive; the larger ones were hemispherical or elliptical, raised above the surface of the skin, soft, and mushy. On the top they were depressed, opened, and discharged a serosanguineous fluid. A necropsy and histological examination showed that the condition was Hodgkin's disease as described by modern writers. The microscopic appearance of the skin tumors was the same as that of the lymph nodes and secondary growths in the spleen and liver. Grosz considers that the condition is different from the various lymphomatoses and sarcomatous tumors which have been described as occurring in the skin, and believes that it is to be definitely distinguished from lymphodermia perniciosa of Kaposi, sarcomatosis cutis, and the group of multiple benign sarcoid tumors of the skin. Gowers mentions the occurrence of hemorrhages in the skin and mucous membranes. This is certainly not as common as the hemorrhages which occur in leukæmia. It is not mentioned once in the 86 collected cases.

Fever.—The fever of Hodgkin's disease is a fairly constant feature, although at times it may be absent and the disease runs an afebrile course. It is customary to divide the febrile cases into three groups. In one class of cases there is a continued mild fever, slightly irregular, varying a few degrees and rarely going above 101° or 102°. This slight rise of temperature may persist for months or even longer, and in certain cases lasts

[1] *Ziegler's Beiträge*, 1906, xxxix, 405.

throughout the disease. But more often during the later stages of the affection the character of the temperature curve changes to one of the other two types. In the second group of cases the temperature is quite irregular, high, and intermittent, showing perhaps diurnal remissions of several degrees. With the elevation of temperature there may be chilly sensations or actual chills, and sweats even when there is no secondary tuberculosis. In the third group the type of the fever is exceedingly interesting. It is relapsing, and periods of pyrexia of several days' or even weeks' duration alternate with longer or shorter periods of apyrexia. This condition may continue for many months. Murchison[1] drew attention to these relapsing fevers in Hodgkin's disease, and later Ebstein[2] and Pel[3] described cases illustrating a condition in children to which Ebstein at first gave the name of "chronic relapsing fever." Pel and, later, Ebstein too decided that these cases were examples of Hodgkin's disease showing a curious type of relapsing fever. Since that time the relapsing type of fever has been frequently observed. It is possible that in such cases the rise of temperature is due to a secondary infection of some sort. Fischer, in one instance, isolated staphylococci in cultures from the blood during the attacks of fever which lasted ten to twelve days, while cultures during the afebrile attacks gave no growth of bacteria. Ruffin,[4] on the other hand, has reported a case in which there were four periods of pyrexia, each of which lasted from ten to thirty-five days, and in which blood cultures during the fever periods always gave negative results.

Blood Changes.—The anæmia, which generally develops as the disease progresses, is one of the characteristic symptoms. It is ordinarily of a secondary type. In long-continued and chronic cases the loss of hæmoglobin and decrease of red blood corpuscles takes place slowly; but when the disease runs a rapid course the anæmia soon becomes marked, and before death it may be very severe. Not uncommonly the hæmoglobin falls to 30 or 40 per cent., and the red blood corpuscles to 3,000,000 or 2,000,000 per cmm. Occasionally the anæmia is of an extreme grade. In one of the cases which occurred at the Pennsylvania Hospital, Philadelphia, the hæmoglobin, some days before death, registered 22 per cent., and the red blood corpuscles numbered 980,000. Nucleated red blood corpuscles are rarely found.

The white blood corpuscles show no characteristic alterations. Their number is not absolutely constant, but, as a rule, these elements, in proportion to the number of red blood corpuscles, are increased rather than decreased. Most frequently the leukocytes vary between 10,000 and 20,000. Of 38 of the collected cases in which a blood count is recorded, the leukocytes in 11 instances were below 10,000, in 21 instances between 10,000 and 20,000, and in 6 instances above 20,000. Pinkus[5] holds that an increase in the small, mononuclear cells is characteristic of the disease, and, indeed, lays a great deal of stress on this point. A review of the recent literature, however, does not seem to uphold his contention. Da Costa[6] states that lymphocytosis is rare, and noted it only three times in his series of 10 cases. Of 31 of the collected cases in which differential counts were recorded, the poly-

[1] *Transactions of the Pathological Society*, 1870, xxi, 372.
[2] *Berl. klin. Woch.*, 1887, xxiv, 565, 837.
[3] *Ibid.*, 644.
[4] *American Journal of the Medical Sciences*, 1906, cxxxi, 587.
[5] *Nothnagel's System*, American edition, "Diseases of the Blood."
[6] *Clinical Hæmatology*, p. 268.

morphonuclear leukocytes in 21 formed over 70 per cent. of the cells at every count; in 4 cases they were above 70 per cent. in one count, and in one case above 70 per cent. in two counts. In only 5 cases did the polymorphonuclear leukocytes persistently form less than 70 per cent. of the white cells. The lymphocytes in 15 cases formed less than 20 per cent. of the total number of white cells, while in only 6 instances were they at any time above 30 per cent. A marked leukocytosis and a relative increase of the lymphocytes never occurred together. In general the blood picture seems to offer nothing characteristic, although for the diagnosis it may be of value and is positively essential in excluding such a condition as lymphatic leukæmia. In a few cases of Hodgkin's disease there is a relative and absolute increase in the eosinophilic leukocytes. In 3 of the cases in this series Pepper found a relative eosinophilia of from 8 to 13 per cent. Lincoln[1] has called attention to this point and discusses the question at some length. The latter author reports a case in which the eosinophiles formed from 43.4 to 70 per cent. of the total number of white cells.

Diagnosis.—Owing in part to the great confusion in nomenclature, but principally to a lack of exact knowledge concerning the nature of the process, a number of conditions have from time to time been grouped under the heading of pseudoleukæmia, which are now considered to be different and distinct diseases. Attention has already been called to the fact that certain observers would still class several distinct pathological conditions under the term of Hodgkin's disease and distinguish certain definite types recognizable by their pathological histology. There are, however, a number of the diseases of the lymph nodes and spleen which with our present knowledge must be definitely distinguished both on clinical and pathological grounds from Hodgkin's disease.

Splenic anæmia and the various forms of *splenomegaly*, once thought by many and considered as late as 1893 by Westphal[2] to be a splenic form of pseudoleukæmia, are now known to be absolutely unlike Hodgkin's disease in their pathological anatomy and symptomatology. The recent work of many writers goes to show that the pathological changes in splenic anæmia are either of a chronic inflammatory nature with connective-tissue overgrowth or consist in the extensive proliferation of tumor-like nodules. Rarely is there any difficulty in distinguishing splenic anæmia from Hodgkin's disease during life. Only in those cases of Hodgkin's disease in which the spleen is greatly increased in size and the enlargement of the lymph nodes is confined to the abdominal groups can any question arise as to the diagnosis between the two conditions. One such case occurred in the Pennsylvania Hospital series. Even so, it may be possible to feel masses in the abdomen on deep palpation; or there may be pressure symptoms such as jaundice, œdema of the lower extremities, or pain in the legs, which lead one to suspect the presence of hidden tumor masses. Any swelling of the superficial lymph nodes rules out splenic anæmia, for in this disease the glands are not enlarged.

The "pseudoleukæmia infantum" of von Jaksch[3] and the "anæmia splenica infectiva" of the Italians are apparently entirely different conditions, and should not be confounded with Hodgkin's disease.

[1] *Boston Medical and Surgical Journal*, Fitz's *Festschrift*, 1908, clviii, 677.
[2] *Deut. Arch. f. klin. Med.*, 1893, li, 83.
[3] *Wien. klin. Woch.*, 1889, Nos. 22, 23, pp. 438, 457.

The group of tumors known as *multiple myeloma*, once termed by certain observers myelogenous pseudoleukæmia, are in no way connected with Hodgkin's disease. The pathology of the condition has recently been discussed by Hoffman,[1] Ribbert,[2] Sternberg,[3] Menne,[4] Lubarsch[5], and Christian.[6] The disease is characterized by multiple tumor growths appearing usually in several different bones of the body. These tumors take their origin from one or another of the cells in the marrow of the bone, but as yet the exact histogenesis is disputed. Meltzer, who in 1904 collected 35 recorded cases, considers that the coincidence of myeloma and albuminuria constitutes the essential features of the disease.

The general glandular enlargement seen in *syphilis* is not liable nowadays to be mistaken for Hodgkin's disease. Tumors of the mediastinum and neck may lead to confusion. In a patient at the Philadelphia Hospital an enormous multilobulated tumor of the thyroid gland was mistaken for a group of enlarged lymph glands, and considered to be Hodgkin's disease until the real condition was discovered at autopsy.

The conditions which may most readily be mistaken for Hodgkin's disease are lymphosarcoma, lymphatic leukæmia, tuberculosis, and acute inflammatory enlargements of the lymph nodes.

In considering the complex question of malignant new-growths of the lymph nodes and their differentiation from Hodgkin's disease, it is necessary to bear in mind certain distinctions which have been made, by such authors as Paltauf and Sternberg, between the various types of sarcoma of the lymph glands, round-cell sarcoma, mixed-cell sarcoma, spindle-cell sarcoma, and the tumors probably arising from the endothelial cells of the lymph glands, from the types of tumor classified by Kundrat[7] as lymphosarcoma, a tumor arising from the lymphoid tissue of the lymph nodes.

The various types of *sarcoma* of the lymph nodes, tumors of rare occurrence, are in general not very difficult to differentiate from Hodgkin's disease. Their growth is rapid, they usually give pain, the tumors infiltrate the surrounding tissue, they may involve the skin, break down and ulcerate, and often form metastases. At times, however, the tumors grow more slowly, forming large, irregular masses in the neck or axilla. The disease may not be accompanied by pain, and the picture resembles very closely Hodgkin's disease. Such a case occurred at the Pennsylvania Hospital, and the true nature of the growth could not be determined until a small superficial nodule was removed for diagnosis. Sections of the tumor showed that it was composed of round cells, larger than lymphocytes, rich in karyokinetic figures and infiltrating fat lobules to form secondary tumors.

The second group of lymph node tumors, *lymphosarcoma*, was originally divided into two varieties; one a localized growth of a single group of lymph nodes, the other a generalized enlargement of lymphatic structures, with infiltrating tumors in various organs. In cases belonging to the second group, it is very frequent to find involvement of the walls of the alimentary canal and serous surfaces. In a large proportion of cases the tumor in-

[1] *Ziegler's Beiträge*, 1904, xxxv, 317.
[2] *Cent. f. allg. Path. und path. Anat.*, 1904, xv, 337.
[3] *Erg. der allg. Path. und path. Anat.*, Lubarsch-Ostertag, 1905, 9th Jahr, p. 441.
[4] *Virchow's Archiv*, 1906, clxxxiii, 115.
[5] *Ibid.*, clxxxiv, 213.
[6] *Jour. of Exp. Med.*, 1907, ix, 325. [7] *Wien. klin. Woch.*, 1893, vi, 211, 234.

vades the wall of the stomach or intestines or grows upon the surface of the pleura. MacCallum[1] has recently discussed this entire question again, and from the study of his cases draws a sharp distinction between lymphosarcoma and Hodgkin's disease on the one hand, and lymphosarcoma and round-cell sarcoma of the lymph nodes on the other.

In lymphosarcoma the tumors, which are composed of cells of the lymphoid type, all of one variety and either of the size of small lymphocytes or somewhat larger, involve entire lymphoid structures, lymph nodes themselves, or the lymphatic tissue of the pharyngeal or intestinal regions. The cells, lying in a delicate reticulum, grow through the capsule, pushing their way and extending into neighboring structures. In the region of the mediastinum, the adrenal glands, or the pancreas, the structures may lie almost buried in a mass of such tissue. Actual metastases to distant organs, explainable by transportation of cells by way of the blood stream or lymphatics, is uncommon.

Since many of these growths occur within the abdomen or thorax, 3 of MacCallum's 8 cases being essentially intrathoracic, although in 2 there were cervical tumors, and 5 being intra-abdominal, it is not usual to confuse them during life with Hodgkin's disease. When, however, the growths are seen in superficial regions, it is unquestionably difficult at times to make an accurate diagnosis, and these particular cases may be mistaken for Hodgkin's disease. At times the evidence of involvement of the pleural or other serous surfaces, which is rare in Hodgkin's disease, and the infiltrating and immovable character of the superficial tumors, will serve as points of differentiation.

The relationship which Hodgkin's disease bears to lymphatic leukæmia is regarded in a different light by different observers. At the time when Hodgkin's disease first began to attract attention, Virchow had long since (1845) published his work upon the leukæmias, and of the early writers, Cohnheim, who proposed the name pseudoleukæmia, and Wunderlich were among the first to recognize an essential difference between Hodgkin's disease and leukæmia. Much later cases were described, such as the one by Mosler,[2] in which there was supposed to be a transition from pseudoleukæmia to lymphatic leukæmia.

Recently several classifications of the so-called lymphomatoses have been proposed in an endeavor to group these conditions together under one heading. It must be remembered that in these classifications the term pseudoleukæmia refers not to the disease under discussion, Hodgkin's disease, but to entirely different affection. Sternberg[3] recognizes a condition that he calls pseudoleukæmia, and which is distinguished from lymphatic leukæmia only through the absence of leukæmic changes in the blood. There is general glandular enlargement, and the lymph glands show the same histological picture as those in lymphatic leukæmia. Pseudoleukæmia, as the term occurs in the other classifications, has much the same significance. Türck,[4] for instance, for some time, has brought under the heading of the lymphatoses the acute and chronic varieties of lymphatic leukæmia,

[1] *Johns Hopkins Hospital Bulletin*, 1907, xviii, 337.
[2] *Virchow's Arch.*, 1888, cxiv, 461.
[3] *Erg. der allg. Path. und path. Anat.*, Lubarsch-Ostertag, 1905, ninth year, p. 441.
[4] *Wien. klin. Woch.*, 1899, No. 40, p. 985; *Berl. klin. Woch.*, 1901, No. 38, p. 965; *Wien. klin. Woch.*, 1903, No. 39, p. 1073.

pseudoleukæmia, chlorosis, and lymphosarcoma, suggesting that the difference between them is rather one of degree than kind; while Pappenheim[1] believes there is no distinct dividing line between leukæmia and pseudoleukæmia as the term is applied by Sternberg. Among these authors, Sternberg as well as Borsh and Bante exclude from this classification of the lymphomatoses the granuloma-like tumor or Hodgkin's disease as an entirely different and distinct process. This is a view which is upheld by all the recent German investigators, as well as certain English and American writers. During the early and even more confused state of our knowledge concerning these conditions, it is probable that cases which would now be termed pseudoleukæmia by continental writers were classed as Hodgkin's disease.

There is indeed still some question as to the existence of the condition which Sternberg terms pseudoleukæmia, a disease resembling in every respect lymphatic leukæmia, except for the lymphæmia. It is well known, and has been emphasized by Gulland,[2] Klein,[3] and others, that during the course of lymphatic leukæmia there may be periods lasting weeks, months, or even years in which there is little or no rise in the total number of white cells of the blood, and at times scarcely any increase in the relative numbers of lymphocytes. During such stages the disease might readily be termed pseudoleukæmia, or without a histological examination of the tumor masses might even be mistaken for Hodgkin's disease, and it is probably to this class that the so-called transition cases from Hodgkin's disease to lymphatic leukæmia belong. To substantiate this belief, Reed asserts that a careful histological study of the tumor masses has not been made in any of these cases. Banti is inclined to regard what is now termed pseudoleukæmia as one stage of a lymphatic leukæmia.

In *lymphatic leukæmia* the glandular enlargement may be well marked, while the spleen may be enormously enlarged, and since in other respects as well this disease may simulate Hodgkin's disease, it may be extremely difficult to differentiate them without a blood examination. But a careful study of the blood, and, if necessary, a prolonged one, will in all cases lead to a correct diagnosis.

Of all types of glandular enlargements the one most often mistaken for Hodgkin's disease is *tuberculosis*. Sometimes, indeed, from a clinical examination alone, it is impossible to tell the affections apart. There are two types of tuberculous adenitis to which particular attention must be paid. One of these is an acute tuberculosis, a comparatively rare form, which may affect the cervical lymph nodes and cause confusion in the diagnosis. In this condition the glands may swell rapidly. One or both sides of the neck may be involved. The enlargement generally begins in the nodes beneath the jaw and in the anterior triangle. As a rule, the nodes are painful or tender, and fever is present at some time. To palpation the tumors are regular, oval, fairly firm, but elastic. They may be readily outlined, separate, and freely movable beneath the skin; so that unless there is a recognizable tuberculous lesion elsewhere, which may give a clue as to the real nature of the lymph gland swelling, it is often very difficult to decide whether one has to deal with tuberculosis or Hodgkin's disease. Even after the tumors are

[1] *Zeit. f. klin. Med.*, 1904, lii, 285.
[2] *British Medical Journal*, 1901, i, 708.
[3] *Zeit. f. inn. Med.*, 1903, xxiv, 817.

removed the macroscopic appearance is at first deceiving. The capsule is perfect and delicate, the surface is smooth and regular, and on section the cut surface presents a yellowish gray appearance, is semitranslucent and bulging. But occasionally small, opaque, yellow points may be observed, and in a cross light one can see that the surface is peppered with minute shiny, raised points. Microscopically the tissue is filled with typical miliary tubercles.

The second and common form of tuberculous adenitis which is so difficult to differentiate from Hodgkin's disease is the generalized caseous type. It is this variety which Fagge described, and to which Delafield, Askanazy, Weishaupt, and Cordua later drew attention. As a rule, in cases of extensive glandular tuberculosis there is a broken-down gland; or the larger tumors are matted together and immobile, while the smaller glands are hard, irregular, and form corded chains. A history may be obtained of glandular enlargement dating back several years, or the scar of a healed sinus discovered. But the class of cases which are so readily mistaken for Hodgkin's disease are different. This form of tuberculosis may imitate Hodgkin's disease almost exactly in its clinical course. The tumors may be very large, and present not only in the neck, but in the axillæ, mediastinum, and abdomen. They are hard, do not break down, often appear as separate masses, and are not attached to the skin. When removed the glands are found to be entirely caseous, with a narrow zone of connective tissue about the margin.

To establish the diagnosis in such cases the tuberculin test may be tried. But even more satisfactory is the removal of a superficially placed gland for microscopic examination. The operation may be readily performed under local anæsthesia, with little discomfort to the patient. By this method a diagnosis is arrived at with absolute certainty.

Prognosis.—Hodgkin's disease is probably fatal in every instance, and the patient rarely lives more than three years. Of 49 fatal cases, 34 died within two years. One patient lived six years and two lived seven years.

During the late stages of the disease the patient presents a pitiable condition. The tumors, perhaps in the neck or mediastinum or axilla, attain enormous proportions; there is cachexia and dyspnœa; the arms are wasted and the abdomen and legs often are swollen. Death may come, as in other wasting diseases, from a secondary infection; or may be mechanical and result from pressure of the tumors upon the trachea, giving rise to asphyxia. Occasionally œdema of the larynx ends the scene. Of the secondary infections, tuberculosis is by far the commonest. It is mentioned as a complication or as the immediate cause of death in 13 of the 86 cases, or in over 15 per cent. Occasionally the patient dies of miliary tuberculosis. General streptococcus infections, acute endocarditis, acute pleurisy, and peritonitis determine the lethal exit in a certain proportion of cases. Rarely death seems to be dependent upon the severe secondary anæmia.

Treatment.—Up to the present time neither medicinal nor operative treatment has been effectual in bringing about a cure of Hodgkin's disease. Arsenic, a remedy said to have been suggested first by Nélaton, has been most generally employed. Following continuous doses of Fowler's solution the glands frequently diminish in size, but the improvement is only temporary and the tumors sooner or later return and proceed to enlarge. The results of operative treatment, which for some time has been in vogue, have not proved of lasting benefit. Removal of a few enlarged glands is of no avail, and even when a complete dissection of the tumors is made there is inevitably

a recurrence, if not at the site of the operation, at least in some other region. Repeated operations have not proved successful. Not infrequently after an operation the glands return in increased numbers, and grow with greater rapidity than before.

Recently, the *x*-rays seem to have been employed with beneficial effect. In this country Pusey[1] and Senn[2] were the first to report improvement under this treatment. Since 1903 the reports of many cases have been published in which *x*-rays have been employed as a method of treatment in Hodgkin's disease and leukæmia. Schirmer,[3] in 1905, collected reports of 21 cases of pseudoleukæmia, and again, in 1906,[4] added 19 more cases to the list, making in all 40 cases. The patients were exposed to the action of the rays over a time lasting from six to eleven months. The immediate results are almost always satisfactory. The tumors shrink away or disappear entirely, sometimes with surprising rapidity, but when the treatment is discontinued the growths return and require a second course of treatment. Pancoast[5] has collected 44 cases from the literature, and finds that although the *x*-ray treatment has not, so far, effected a cure, it does prolong the life of the patient. Of 29 of the 44 cases in which final reports have been received, 24.1 per cent. have lived for from three to four years after the first symptomatic cure. Unfortunately, such accidents as dermatitis and superficial burns are common, for the exposure, in order to be useful, must be long continued and applied over large surfaces.

According to Stürsberg,[6] the disappearance of the glands under the influence of the *x*-rays is accompanied by certain slight changes in metabolism, which, however, are quite different from the alterations that take place under the same method of treatment in leukæmia. Following directly upon the first exposure of the rays the total quantity of purin bodies falls slightly. From this time forth there is a gradual and persistent rise, until after some time the total amount of purin bodies is distinctly increased above that eliminated before exposure. Pancoast reports the results of metabolism investigations upon one of his cases. The total output of nitrogen, uric acid, chlorides, and P_2O_5 was estimated. For the first twenty-four hours after the treatment was started the waste products, with the exception of the nitrogen, showed a decrease below the average of the preliminary control period. On the second day there was a recovery, and for the first four days of treatment the average showed an increase in P_2O_5 and nitrogen, and a decrease in uric acid and chlorides.

The manner in which the *x*-rays act upon the glands in Hodgkin's disease is made clear by a series of experiments which Heineke[7] has performed upon animals. He found that when guinea-pigs and white mice are exposed to the action of the *x*-rays all the lymphoid tissue of the body is very rapidly destroyed. In the lymph glands the small lymphocytes show chromotolysis, and if the exposure is continued for a sufficient length of time the lym-

[1] *Journal of the American Medical Association*, 1902, xxxviii, 166 and 917.
[2] *New York Medical Journal*, 1903, lxxvii, 665.
[3] *Cent. f. d. Grenzg. der Med. und Chir.*, 1905, viii, 31, 56, 98.
[4] *Ibid.*, 1906, ix, 561, 609.
[5] *University of Pennsylvania Medical Bulletin*, 1907, xix, 282.
[6] *Med. Klinik*, 1906, ii, 192.
[7] *Mitth. aus der Grenzgebiete der Med. u. Chir.*, 1904, Band xiv, Heft 1 and 2; *Deut. Zeit. f. Chir.*, 1905, lxxviii, 196.

phocytes rapidly disappear. And since cells other than lymphocytes are left unharmed, this action of the *x*-rays is, to a certain degree, specific. The destructive action is, however, not permanent. After the exposures have been discontinued, lymphocytes reappear and lymph glands regenerate. Warthin,[1] in a similar series of experiments, has obtained practically the same results. Heineke has found, moreover, that not all cases of Hodgkin's disease respond with the same alacrity to the treatment by the *x*-rays. This difference he considers is due to a difference in the structure of the glands. Tumors of the soft type, which are cellular, and in which most of the cells are lymphoid cells, disappear rapidly after exposure to *x*-rays, while tumors of the hard type, in which the growth is composed principally of connective tissue, are scarcely, if at all, influenced. Unfortunately, no cure is known for this terrible disease, but at least we have a method of prolonging life and perhaps for combating the secondary pressure symptoms which are looked upon with so much dread.

[1] *International Clinics*, 1906, iv, 243.

CHAPTER XXI.

ARTHRITIS DEFORMANS.

BY THOMAS McCRAE, M.D.

Introduction.—It is necessary for anyone writing on the subject of chronic arthritis to state definitely, so far as possible, what conditions are included under various terms and what is meant by the designations employed. It is well to confess without any hesitation that our knowledge of chronic diseases of the joints is in an unsatisfactory condition, and that great difference of opinion exists on many points. In any expression of opinion and discussion we should keep an open mind, for the work of the future will probably change many of our views. The best that one can do at present is to put forward his views in such a form that others can at any rate understand what is meant, and if they disagree have no difficulty in recognizing where the difference lies. Much of the pathological and clinical material is a matter of record; the conclusions drawn are more or less matters of opinion.

In this article the designation arthritis deformans is used to include the group of cases of arthritis which have as prominent features a tendency to chronicity and to more or less permanent change in the joints or structures about the joints, those forms of arthritis with a definite etiology (*e. g.*, gonorrhœal arthritis) being excluded. That this is a satisfactory classification cannot be held, but it seems the best we can have at present. Thus, in many cases of gonorrhœal arthritis there may be chronicity with more or less permanent change in the joints, yet here we have a definite etiology by which they can be classified. Determine a definite etiology for any case or group of cases and they can be separated from the general class. This is what the future may do.

Taking arthritis generally we can divide the various forms into:

1. Traumatic arthritis.

2. Arthritis due to infection with definite bacteria, such as the gonococcus, streptococcus, tubercle bacillus, pneumococcus, etc., which can often be obtained in the joint. It is to this group that the term infectious arthritis properly belongs. It is probable that rheumatic fever belongs here, as the evidence for it being due to infection with a specific organism is very strong.

3. Arthritis occurring in certain diseases, such as scarlet fever and syphilis, and apparently dependent on the cause of the disease, although in some cases it may be due to a secondary infection.

4. Gout.

5. Arthritis due to the injection of various sera, such as diphtheria antitoxin.

6. Arthritis secondary to disease of the nervous system, as locomotor ataxia and syringomyelia. In these trauma may often play a part.

7. Arthritis in hæmophilia, purpura, etc.

8. When all of the preceding are separated a large group remains, the cases of which for the present are put together. In doing so we may be in the same position as clinicians were one hundred years ago, in considering certain acute fevers as an entity, which later observations showed was quite wrong. In this group there is almost an endless variety, many of them showing acute features at times, others being chronic throughout; the degree of involvement varies greatly, but in all there is the predominant feature of a tendency toward some permanent change in the joint or structures about the joint. In this article these cases will be discussed under the heading of arthritis deformans. The designation chronic polyarthritis might be used almost as well as the one chosen.

That there can be any confusion as to the essential nature of the disease as compared with, for example, gonorrhœal or tuberculous arthritis does not seem likely to the writer. Suppose we have regarded a patient as having arthritis deformans and subsequently find gonococci in a joint. That case is removed at once to a definite class, just as if we found streptococci, pneumococci, or tubercle bacilli. One may object and say that the group designated as arthritis deformans simply consists of those cases with certain forms of chronic arthritic change in which no definite etiological factor can be found. This objection, if it be such, is perfectly correct. When we have a definite, proved etiological factor for all forms of arthritis one kind of classification will be perfectly easy. For the present we are doing what we can to make the best of a bad job. It is important to remember that arthritis is almost always *secondary* to a process elsewhere; the joint condition is not the primary manifestation.

Have we in this group one disease or two or more? Many workers are taking the latter view. Thus, in a recent article by A. E. Garrod[1] the view is taken that we are dealing with several maladies (*e. g.*, rheumatoid arthritis and osteo-arthritis) and not with a single disease. This view is held by many authorities. The question is a difficult one to settle. There is no doubt that certain cases of arthritis show features which seem to demand their being considered as distinct entities, but others are found which seem to belong to both groups or to lie between them, showing evidences of both. In all chronic joint changes it is well to keep in mind that the same cause may produce varied results, and the same result may come from different causes. The great variation in the picture presented by arthritis due to a particular organism (*e. g.*, the gonococcus) might easily lead to the severe and mild cases being regarded as different, did not the common cause group them together etiologically. So in this class of arthritis deformans the writer feels that there are so many different grades of change, which merge the one into another, that a classification into distinct diseases from anatomical features is not justified. Their discussion is certainly made much easier if the division into distinct diseases could be accepted.

"*Infectious Arthritis.*"—This term has been used in different ways. Some apply it to certain forms of arthritis which come under the designation of arthritis deformans as given here. These are the cases of arthritis which occur secondary to some focus of local infection, such as tonsillitis, pelvic inflammatory disease, otitis media, etc., but in which no organisms are found

[1] *A System of Medicine*, Allbutt and Rolleston, revised edition, vol. iii.

in the joint. Is this designation a good one? The writer thinks not, for various reasons. The term is with propriety applied to such forms as gonococcus or tuberculous arthritis, in which the etiological factor is definitely proved. To use it for cases in which the cause is not established must lead to confusion. Then by some an "infectious" group is separated, that is, on supposed etiological grounds, while other groups, such as atrophic and hypertrophic, are separated on anatomical grounds. This is not meant to imply that those forms occurring secondary to tonsillitis, for example, are not due essentially to an infection in some way or other, but the evidence seems about as strong for the atrophic and hypertrophic groups. There is no uniformity in the use of the term, for some use it only for arthritis which is due to a definite infecting organism, while others use it both for this and for the group of cases here described under the heading of the peri-articular form and by some writers termed rheumatoid arthritis. For the cases occurring secondary to a focus of infection, without the presence of organisms in the joints, the terms toxic, autotoxic, or toxæmic might be used.

By no means all the cases of arthritis occurring with various local infections (*e. g.*, tonsillitis) are to be regarded as belonging to the arthritis deformans group. Many of them are temporary and recovery follows without there being any evident permanent change in the joint. It is a question, however, whether repeated attacks of this kind would not always leave some damage in the joint. To decide where the line is to be drawn is difficult. The writer feels that if any change is left in a joint the condition probably belongs under the heading of arthritis deformans; the milder cases are probably better considered as secondary complications to the original condition and might be designated as toxic arthritis.

"*Chronic Rheumatism.*"—It seems well to state that in the view of the writer there is no advantage and every disadvantage in the use of this term. We have suffered and do still suffer from the use of the word "rheumatism." Some employ it as synonymous with arthritis of any form, others for rheumatic fever. If it is used as a synonym for arthritis, then its use for a special form of arthritis should be stopped; as well use the term fever for certain febrile diseases and for one special febrile disease. It seems much better to use the term for rheumatic fever only. If this be done there is no reason for the term "chronic rheumatism," for there is no evidence or proof known to the writer that acute rheumatism passes into a chronic condition.[1] To apply the term chronic rheumatism to certain ill-defined joint changes is only misleading; call them chronic arthritis and then there is no suggestion that they have anything to do with rheumatic fever. The use of the word "rheumatism" to describe any form of ill-understood pain—muscular, arthritic, synovial, or neural—is a diagnostic sin for which no good word can be said.

Terminology.—The designations of a whole or part of this group which have been employed are various, and sometimes it is difficult to know exactly how much is included by any particular one. Among them are: Rheumatic gout (Fuller); chronic rheumatism of the joints (Todd); rheumatic arthritis (Adams); nodosity of the joints (Haygarth); rheumatisme chronique

[1] Certain cases of rheumatic fever in children may drag on for months, showing one manifestation after another, and to these the term "chronic" might be applied, but this is not its common use.

primitive (Charcot); goute asthénique primitive (Beauvais); rheumatoid arthritis (Garrod); osteo-arthritis; arthritis sèche; arthritis deformans (Virchow). We have no uniformity in the name used to designate this disease; in Britain the term rheumatoid arthritis is widely used for a certain form. There is much to be said for the use of the designation "chronic arthritis," as it does not commit one to any view as to the nature of the disease. Against this the criticism may be passed that the process is often acute at its onset or at times during the course. The fact remains, however, that essentially the tendency is toward some degree of chronic change in the joints.

In the confusion which involves the whole subject at present, it is perhaps wise to regard this group of joint conditions as best described by the designation chronic arthritis, recognizing that we may have to separate various groups in the future. Of course, it is evident that there are cases of chronic arthritis which do not belong here (*e. g.*, tuberculous arthritis), but these have a definitely established cause, and so can be readily put in their proper place.

Nature of the Disease.—It is evident that so long as there is doubt as to whether we are dealing with one disease or more than one, there can be no agreement as to what the disease essentially is. To recount the various theories in detail is not necessary. A relationship to rheumatism and gout, an inherited arthritic diathesis, a special kind of degeneration, disturbed nutrition, an inflammatory process, of essential nervous origin, due to injury, reflex irritation, or disease of a supposed joint centre and some form of infection, have all been suggested at some time or other.

At present, the view which seems most reasonable is that the disease is dependent on an infectious process of some kind. This is not to be interpreted as meaning a definite infection of the joint with organisms. This may occur, but in many cases the arthritis seems to be dependent on local infection in some part of the body, with perhaps absorption of toxins and a secondary arthritis. How far possible absorption of toxins from the intestines may be a factor we are not in a position to state. It seems that in many instances the factors of trauma, wear and tear, and the tendency to degenerative changes in the joints of those advanced in life must be kept in mind as additional factors. Changes due to an infectious process, which may be subacute or chronic, may be associated with any of these.

The view of the disease suggested here is that the arthritis is due to an infection of some kind—probably this may be with many different organisms—as a result of which very varied changes may result. The arthritis is probably always a secondary process. The changes involve especially now one and again another part of the joint, with a great variety of results, individual reaction and resistance probably playing a large part in determining the essential changes which follow. As to how far inherited tendencies may affect the process it is difficult to say. Some families seem to have joints which are more susceptible to infection and degeneration.

Classification.—As already mentioned, there is much difference of opinion as to whether we have one or two or more diseases in this class. Some writers emphasize the distinction between the form in which the bony changes predominate and that in which the changes are more in the cartilage and structures about the joint. That in many cases this is true there can be no doubt, but it does not seem to be true so invariably that it can be used to

prove the existence of two diseases. Thus, when one finds a patient showing changes of one form in one joint and of another form in a second joint, the inference is that he has the one disease manifesting itself in different ways. It is possible that two diseases may co-exist, but this is too uncommon to explain the frequency of these cases. Thus, the patient may have marked osteo-arthritic changes in the spine, with distinct hypertrophic changes, and in the peripheral joints, well-marked change affecting the structures about the joint. Again, in a patient whose predominant changes are peri-articular it may be possible to find distinct hypertrophic changes in some situations. The writer feels that there are so many examples of these mixed cases that they offer a great objection to the adoption of the view that different diseases can be distinguished. Certainly, if this distinction between the "osteo-arthritic" and "rheumatoid" could be granted, it would simplify the discussion of the subject very greatly, but there seems to be much against it. That there are striking general differences between typical cases in each group is very true, but are there not just as marked differences between cases in the same group?

For clinical study, it is convenient to make a classification without regarding the forms as distinct diseases. The character of involvement varies, and, as a rule, certain features predominate. This, however, is not always true, and it may be difficult to decide in which group to place a given case. In some of this series it was difficult to decide whether bony changes or those in the peri-articular tissues predominated. In other cases a single joint may show various changes.

In this article certain groups are distinguished for convenience of study, it being understood that the lines between these are not definite, but, as a rule, enable one to put a given case in one of them. As already said, some cases (45) seem to belong to two of them and cannot be definitely classified. The division here used is into three groups:

1. A form in which the changes predominate in the structures apart from the bony parts of the joint, although the cartilages are frequently involved to some extent. The degree of change varies greatly. This group is termed "peri-articular," and in this series 240 cases were regarded as belonging to it.

2. A form in which the chief change consists in marked atrophy both of the bones and cartilages. With this there are usually marked trophic changes in the muscles. This is termed the "atrophic" form, and comprised five cases.

3. A form in which hypertrophic changes are the most prominent. There may be marked bony overgrowth, which may occur at the edges of the articulating surfaces especially, or in the spine, involving the cartilages and ligaments. This is termed the "hypertrophic" form, and sixty cases belonged to it.

The question arises as to whether one of these forms may pass into another. As a rule, this does not seem to occur, although in some cases the course suggests that cases showing the changes of the peri-articular form may later have those of the atrophic type. Thus, in one patient of this series the changes when she was first seen were entirely of the peri-articular form, the bones and cartilages being entirely free; a year later the picture was much like that of the atrophic form. Many factors have a possible bearing: atrophy from disuse (which, however, gives a different picture), secondary trophic

disturbances, marked general toxæmia, etc. As stated, in some patients there may be a combination of conditions, and it may be difficult to say to which group the patient belongs. There were forty-five such cases in this series in which it was impossible to classify the condition with any certainty.

Historical.—While the history of the malady as a separate entity does not extend far back, yet the disease itself is the oldest in the history of the human race of which we have definite proof. This record is not found in books but in bones. When the bodies of those who had suffered from the disease were placed in the tomb, they contained evidence which was to come to light centuries later. The characteristic changes of the disease have been discovered in bones found in Egypt, which are considered to date back to 1300 B.C. (Petrie). From Egyptian tombs, from Roman graves in Britain, from Pomerania, from Pompeii, from the catacombs of Paris, have come bones showing the changes of this disease.

The very early medical writers used the term arthritis to include a wide variety of joint infections. It is difficult to separate these, but in some of the earlier writers (such as Aretaeus) there are allusions to chronic joint changes which are other than those of gout. Judging from his descriptions, Paulus Aeginata must have observed the lesions of arthritis deformans and suggested in a way their distinction from gout. To Ballonius (1642) is ascribed the introduction of the term "rheumatism," but regarding the confusion which has arisen from its use it may not be considered as greatly to anyone's credit. The description given by Sydenham suggests very strongly that he recognized arthritis deformans, which he discusses under rheumatism; certainly, the chronicity and the tendency to deformity are well described. In 1800 Landré Beauvais published, under the title "Goutte asthenique Primitif," a description of this disease. But the credit of the first endeavor to separate arthritis deformans as a distinct disease seems to belong to Heberden and Haygarth. Heberden[1] says: "The disease called the chronical rheumatism, which often passes under the general name of rheumatism, and is sometimes supposed to be gout, is in reality a very different distemper from the genuine gout and from the acute rheumatism, and ought to be carefully distinguished from them both. The chronical rheumatism for a few days appears to be a milder distemper than either the acute sort or the gout: but in its consequences, that is in the great weakness or total loss of power it produces in the limbs and in the mischief done to the general state of the body, it is much more formidable than either of them; and being so very different in its symptoms, as well as in the event, it would be useful if it were distinguished by a peculiar name which might prevent its being confounded with other disorders by being called a spurious and wandering gout or a chronical rheumatism." It is fitting that Heberden's name should be preserved in association with one of the manifestations of the disease.

A little later Haygarth[2] (1805) emphasized the same points and aptly said, "The term rheumatism has been applied without sufficient discrimination to a great variety of disorders, which, except in pain, have but few symptoms

[1] *Commentaries on the History and Care of Disease*, 1803, second edition.

[2] *A Clinical History of Acute Rheumatism. A Clinical History of Nodosity of the Joints*, 1805.

that connect them together." He suggests that one form of chronic arthritis should be separated, and for this he suggests the name of "nodosity of the joints." This designation does not seem to have been applied by him to any special manifestation of the lesions, but to the deformity in all the joints. Doubtless it was suggested by examples of marked deformity. A few years later (1812)[1] he again emphasized the difference between this condition and chronic rheumatism. Brodie[2] regarded the disease as gouty in nature, while Scudamore (1827) considered that it was a variety of chronic rheumatism. The observations which he made and the descriptions given leave no doubt that he recognized its essential features. He pointed out the definite alterations in structure in the joints.

There are many writers about this time who described the disease and its lesions accurately. Budd, Todd, and Watson all inclined to regard the disease as essentially rheumatic in nature. However, about 1850, the view that there was a disease distinct from both rheumatism and gout began to gain ground, and Fuller (1852) emphasized this, terming the disease "rheumatic gout." Colles pointed out that there were two processes at work, one of absorption and one of formation of bone. Adams (1857), in his classical *Atlas*, inclined to the same view, suggesting the name "chronic rheumatic arthritis," and Garrod, in 1859, supported this and suggested the name "rheumatoid arthritis." Rokitanski, in 1856, considered it as probably a variety of rheumatism. Virchow, in 1859, proposed the name of arthritis deformans.

The views held in the last fifty years have shown great divergence. Many of the English writers especially have considered it essentially related both to gout and rheumatism, others have laid stress on the importance of an arthritic dyscrasia which might manifest itself in various ways, now as gout, now as rheumatism, and again as the disease under discussion. Naturally, as long as the question of a distinct disease was unsettled, no clear idea as to its cause could be held. For a time the idea was widely held that the essential cause was in the nervous system, and that the arthritic manifestation was secondary to this. The marked muscular atrophy, changes in the reflexes, and the frequent trophic disturbance were looked upon as supporting this view. The weight of opinion, however, is now coming to the view that we have in arthritis deformans a disease distinct from gout and rheumatism, and in the majority of cases showing a definite clinical and pathological picture. Naturally, with such divergent views as to its nature, any clear idea as to the etiology could not be expected. As regards this there have been widely different opinions, but the tendency of the majority of those who have studied the disease is to regard it as essentially due to infection of some sort. To-day this may be considered as the view most in evidence and the one most strongly supported.

When we consider the history of our knowledge of disease generally, it is not surprising that the views regarding arthritis should have gone through the same stages as those, for example, regarding the fevers. At first grouped together under one heading, with the increase of knowledge one after another was separated and given its own identity. Exactly the same has occurred with arthritis, and it may be that we have not reached the end of this process.

[1] *Medical Transactions of the College of Physicians*, vol. iv, p. 294.
[2] *On Diseases of the Joints*, 1818.

The future may see still further divisions of the condition here considered as arthritis deformans, and it is well to have an open mind in this regard.

Etiology.—The various general factors are as follows:

1. **Sex.**—The figures given by various writers vary greatly, but in the majority of statistics the larger number is said to belong to the female sex. One factor which makes a material difference is whether the cases of spondylitis are included or not. They are usually in males, and if included make the numbers in the two sexes more nearly equal. Without doubt there is some difference in the relative occurrence of the various forms in the sexes. In the present series of 350 cases,[1] 178 were males and 172 females, all the cases of spondylitis being included. In a series of 1228 reported cases collected by the Cambridge Committee,[2] it was found that 76.5 per cent. were females and 23.5 per cent. males.

2. **Age.**—It is important to remember that the age of patients when seen may give a false idea of the time of greatest prevalence. The disease is so chronic that in any clinic many patients come with advanced changes years after the onset. It may be said that the disease can occur at any age except in early infancy. The Cambridge report mentions one case beginning at eighteen months. The more carefully the histories of those in whom apparently the disease begins at an advanced age are studied, the more often it will be found that there has been some arthritis before. Still, the first manifestations may be after the age of eighty years. To obtain a true idea of the greatest occurrence, therefore, the age at onset should be noted. The records in this series as to the age when the patient came under observation are as follows:

	Number.	Percentage.
1 to 10 years	4	1.1
11 " 20 "	18	5.1
21 " 30 "	68	19.4
31 " 40 "	90	25.7
41 " 50 "	64	18.2
51 " 60 "	57	16.2
61 " 70 "	37	10.5
71 " 80 "	10	2.8
81 " 90 "	2	0.6

The age of onset shows that in 45 per cent. this was below the age of thirty years, while only 25 per cent. were below the age of thirty on admission. The largest number is in the third decade. The figures as to the time of onset are:

[1] The series, which is used as the basis of this article, is composed of the records of patients in the Johns Hopkins Hospital and a number personally observed elsewhere. The report of 110 of them has already been published (*Jour. of the Amer. Med. Assoc.*, 1904, xlii, 1, 94, 161).

[2] *Bulletin of the Committee for the Study of Special Diseases*, Cambridge. This is the report of the work already done in a special investigation of this disease. It should be studied by all those interested in the subject. It will be referred to here as the Cambridge report.

	Number.	Percentage.
1 to 10 years	18	5.1
11 " 20 "	53	15.1
21 " 30 "	84	24.0
31 " 40 "	73	21.0
41 " 50 "	53	15.1
51 " 60 "	40	11.4
61 " 70 "	18	5.1
71 " 80 "	3	0.8
81 " 90 "	0	0.0
Doubtful	8	2.3

Here, again, the type of disease has some influence. The peri-articular and atrophic forms usually come on earlier than the hypertrophic, which is more often characteristic of the older patients. The changes of this type in the larger joints are especially common in elderly people.

With these figures may be compared those of Bannatyne (293 cases), Garrod (500 cases), and the Cambridge report (200 cases) as to the age of onset.

	Bannatyne.	Garrod.	Cambridge.
1 to 10 years	0	3	5
10 " 20 "	19	22	20
20 " 30 "	59	64	46
30 " 40 "	86	85	38
40 " 50 "	61	121	39
50 " 60 "	54	90	34
60 years and over	14	80	18
Doubtful	0	17	

It may be noted that of Bannatyne's series, 86.1 per cent. were females and 13.9 per cent. males, and of Garrod's patients, 82.2 per cent. were females and 17.8 per cent. males.

3. **Race.**—This is of special interest in regions where the colored race is a factor. In this series there were 332 whites and 18 colored, a proportion of eighteen to one. This is relatively a low proportion of colored patients, the total medical admission of white to colored in the Johns Hopkins Hospital being about five to one. This is of importance in regard to the influence of certain diseases in the etiology. Thus, the great majority of members of the colored race have had a gonorrhœal infection, and tuberculosis is very common among them. It is interesting to note that they show a higher relative incidence of acute rheumatic fever than the whites and a much lower relative incidence of arthritis deformans. It is not easy to suggest any explanation of this.

4. **Station in Life and Occupation.**—There was no evidence in this series to suggest that any station in life showed a special influence. The patients came from the wealthy and the poor classes in about an equal relative proportion. Nor does occupation seem to have any great influence. Certainly unusual exposure to wet or weather was not marked in this series, and the frequent occurrence among washerwomen, so often commented on by English writers, was not evident. The largest number of the patients lived indoor lives, which raises the question as to whether this may not lower their resistance and predispose to infection, or, at any rate, render them less resistant to a slow chronic infection once acquired.

5. **Alcohol.**—A history of the use of alcohol was obtained from 92 patients, of whom 75 could be described as moderate and 17 as heavy users.

6. **Previous Infections.**—With the view now generally held that the changes are due to some form of infection somewhere, the possible causal relationship of previous infections has always to be remembered. Measles is by far the most frequent of the common diseases recorded in the previous history, but this cannot be regarded as standing in any special relationship, usually having occurred years before. Infections occurring shortly before or about the time of onset are important. Of these, some are striking in the close relationship. Four cases of infected wounds are especially remarkable; it is not necessary to say that in none of these was the arthritis suppurative. Boils were associated with the onset in 4 cases, cystitis in 4, dysentery in 6, pelvic inflammatory disease in 12, otitis media in 4, a pyonephrosis in 1, a miscarriage in 2, and bronchitis in 2.

Of particular diseases, influenza and tonsillitis are of special interest. Influenza had occurred in 18 patients and tonsillitis in 32. The figures for influenza (5.1 per cent.) are lower than in the Cambridge report, in which 9 per cent. was found. In the same report the percentage for tonsillitis was 24; in the last 200 cases of this series in which this point was carefully followed there were 31, or about 13 per cent. In two others there had been frequent attacks of severe pharyngitis. The tonsillar conditions are usually due to infection with some form of streptococcus, and it is well to recognize that tonsils which are not especially enlarged may contain foci of suppuration in their deeper parts, so that infection from this source may be more frequent than these figures indicate. To gonorrhœa some writers have ascribed importance as an etiological factor. Thus, in the report of cases from Montreal, the late James Stewart found a history of gonorrhœa in 40 per cent. of the patients. In this series it was given in 54 cases, or 15.4 per cent. If it was an important factor one would expect to find more arthritis deformans among the negroes, few of whom escape gonorrhœa. Of course, instances of gonorrhœal arthritis are excluded from this series. There was a history of syphilis in 16 cases and of chancroid in one. Scarlet fever, erysipelas, typhoid fever, pleurisy, osteomyelitis, all occurred in a few cases shortly before the onset.

7. **Gastro-intestinal Conditions.**—Pyorrhœa alveolaris and carious teeth may be the source of infection in some cases; the Cambridge report gave these in over 50 per cent. of the cases. Pyorrhœa alveolaris is so almost universal among the lower classes, and so common among the better classes, that figures of its frequency cannot have much significance. Dyspepsia and constipation are common, but often seem to be secondary to the disturbance of the general health. Diarrhœa was present before the onset in 7 instances and dysentery in 4.

8. **Trauma.**—In some cases this seems to have an influence, but probably more often in determining the joint in which the symptoms are first evident than the onset of the disease. There is no doubt that in some cases the first manifestations of the disease are wrongly diagnosed as due to trauma. It is often easy for a patient to remember some strain or fall about the time of onset. However, in one form, spondylitis, the influence of trauma seems well established, just as in spondylitis following typhoid fever. In other cases the effect of an occupation which throws special stress on particular joints seems to determine entirely the early onset or greater severity there. In this series there was a definite history of trauma at onset in 15 cases. In 8 cases the disease was of the peri-articular type, and in 5 of these the joint

injured was the first one to show arthritis. In 7 cases of spondylitis the association of the injury and the onset was clear. Of course, in this there is the likelihood that there was some arthritis already present which was aggravated by the traumatism.

9. **Anxiety and Mental Strain.**—The history of prolonged worry, severe strain and anxiety, troubles of various kinds, etc., is frequently given by the patients (26 per cent. in the Cambridge report). It is often evident that these factors have resulted in lowered health, and it is easy to see that this may render them more susceptible to infection, especially if this be associated with increased work and loss of sleep, as in the nursing of sick relatives. In patients who have the disease the influence of these factors in determining recurrence is only too evident, but here it may be due to the effect in the general health.

10. **Family History.**—This is a difficult matter to speak of with certainty. Is there such a thing as an arthritic diathesis? There are many authorities who firmly believe that there is, and yet the matter is difficult of proof. In this series there was a definite family history of arthritis in 79 cases; of these, 17 were apparently arthritis deformans; 11 were termed rheumatism, and of these a considerable number were arthritis deformans; 3 were acute rheumatic fever, and 3 gout, the others being doubtful. Some patients gave a remarkable family history of arthritis deformans. Thus, in one, the father, three brothers, and three sisters all had the disease in a chronic form; one sister escaped. The patient's mother did not have the disease, but her mother and all her brothers and sisters had. The writer knows of one family of six in which every individual had a deforming arthritis of the slow progressive type, some being almost entirely crippled, others having only some inconvenience. One patient gave a history of the disease in four generations. There was a family history of tuberculosis in 72 instances.

11. **Predisposing Causes.**—While it is often difficult to decide with certainty how much influence these may have, yet in some instances the association is so close that they must be given in place. This is seen not only in regard to the original attack, but also in recurrences. With a patient under observation who has had attacks of the disease, one may be able to predict that with certain events, such as an intercurrent attack of illness, the arthritis is likely to light up. While this is perhaps most marked in the group with peri-articular changes predominating, yet it is also true of those with more marked bony changes. Among these predisposing causes come first those which affect the general health, such as poor hygiene, unsanitary surroundings, hardships, etc. All appear to have an effect. In women the menopause is often of importance, and in fifteen of the female patients (8.7 per cent.) the disease began about the menopause. This association is seen both in attacks beginning at the menopause and also in women who have had the disease in earlier life, and perhaps almost entirely recovered, in whom the symptoms again become active at this time. Frequent pregnancies seem to have an influence in some patients. The onset may come after frequent childbearing, or, more commonly, pregnancy after the disease is once established may apparently cause a lighting up of the process. The infections also are important. These may be of any kind. Influenza and acute bronchitis, an acute dysentery, or pelvic disease may be quoted as examples. How often exposure, wetting, etc., are factors it is hard to say, but the impression gained from the study of this series is that these do not occupy an important etio-

logical relationship. A history of exposure which seemed to stand in a causal relationship was obtained in only seventeen instances. Six patients had lived or worked in damp surroundings. How much importance gastro-intestinal disease may have is difficult to say. It may influence the general health, and so predispose to infection.

However, it must not be thought that predisposing causes are always present. The disease may begin in those who are apparently in the best of health.

12. **Specific Cause.**—As long as there are so many undecided points regarding the disease, it is evident that we are ignorant of the true cause. Perhaps the statement might be reversed, and better put that as we are ignorant of the cause, we have so much obscurity as to the real nature. To take up all the suggestions as to the etiology is useless, but one should be mentioned only to be dismissed—namely, that it is of nervous origin. This can hardly be held any longer, especially in view of the evidence suggesting that the disease is essentially due to some infectious agent. The points which support this are as follows:

(*a*) *The Character of the Attacks.*—These often suggest an acute infection. The sudden onset, the inflammatory local changes, the fever, the presence of complications, such as endocarditis, pericarditis, and pleurisy, and the tendency to run a certain course are all suggestive. These features are not constant or invariable, neither is the usual picture of any infectious disease.

(*b*) *The Similarity of the Lesions to those Proved to be Due to Infectious Processes.*—This is seen in the likeness of the lesions in certain joints to those caused by the gonococcus, for example. This is also true of the bony changes; thus, the picture presented by spondylitis is exactly like that of the spondylitis in typhoid fever or that which may follow a gonococcus infection.

(*c*) *The Definite Association between a Focus of Infection and Arthritis Deformans.*—The examples of this are sometimes very striking. Thus, in one patient seen by the writer the deforming arthritis followed a suppurating joint. When this was properly treated the general arthritis improved rapidly, but some deformity was left. Some would say that this was more properly termed "infectious arthritis," but the writer considers all of this group as due to some infection, and this arthritis certainly was deforming. The same thing may apply to the forms with marked bony changes, as in a case reported by Baer in which an acute arthritis of the spine subsided rapidly after proper treatment of a local focus of infection in the nose. In some cases of chronic arthritis associated with bronchiectasis, the joint condition varied with that of the bronchiectasis.

A number of investigators have described particular organisms which were regarded as being the cause of the disease, but none of these can be accepted as proved.

13. **Nervous System.**—The view was and is still held in many quarters that the cause must be in some changes in the nervous system. There is much against this other than the evidence which speaks for an infection. The similarity to the joint lesions found in chronic disease of the nervous system is only true of the later stages of some forms of arthritis deformans. The joint lesions should correspond to certain segments, but they do not. Then, too, the examination of the central nervous system has not shown any changes to account for the arthritis.

14. **Intestinal Infection.**—It seems possible that in some patients the intestine may be the source of a long-continued infection either by the entrance of organisms, which can perhaps hardly be termed pathogenic under ordinary conditions, or by the absorption of toxins. It is possible that the total sum of repeated slight changes may be due to this. The frequency of the presence of foci of infection in the mouth may be of importance as the influence of the continued swallowing of large numbers of streptococci as a factor in various diseases has been suggested and seems worthy of consideration in arthritis deformans.

As to the possibility of the absorption of toxins from the intestine, one hesitates to attach too much importance to this. Our knowledge of "auto-intoxication" is not satisfactory. One therapeutic point is of interest, however, in this connection; some patients are markedly improved by very free continued purgation. In others, a sharp attack of diarrhœa may result in an immediate gain in the arthritic condition. This can only be regarded as a suggestion and not by any means as an established fact. In some cases of chronic nephritis absorption of toxins from the intestine is regarded as the causal factor.

15. **Relation to Rheumatic Fever.**—Does a condition such as we have in arthritis deformans result from rheumatic fever? Some of the English writers describe cases of rheumatic fever in which permanent arthritic changes appear and persist. The writer can only say that while he has for some years been looking for such cases, he has never succeeded in finding one. He has seen cases which had been regarded as rheumatic fever in which chronic changes were present, but it has always been possible to show that they had been arthritis deformans from the onset. Thus, thickening from a previous attack may be found in some of the joints, or the clinical course may speak against rheumatic fever. However, one positive case is worth more than negative evidence, but judging from the experience of the medical clinic of the Johns Hopkins Hospital, the positive cases are rare in its locality.

16. **Metabolism.**—In the minds of many of the laity and of the profession the cause is supposed to be in some disturbance of metabolism. This is shown by the frequently given opinion that uric acid is the causal agent and by the common reduction in the nitrogenous diet. There does not seem to be the slightest evidence from any source in support of this fact. Clinically the results of a reduction in the nitrogenous intake are usually harmful, and these patients generally do better on a full nitrogenous diet.

Is there any evidence that metabolic disturbances are at all responsible? That such disturbances do occur is well known, but are these a cause or a result? There is no evidence to show that nitrogenous metabolism is at fault, as the studies of this have given negative results. It has been suggested that some derangement in carbohydrate digestion may be a factor in some cases. Some patients are undoubtedly made worse by large amounts of carbohydrates, but this seems due more to intestinal disturbances. That this may be associated with the absorption of toxins is perhaps a tempting suggestion, but we have no evidence to support it. The most reasonable view seems to be that any metabolic changes are a result and not a cause.

17. **Experimental Arthritis.**—Cole[1] has described the lesions produced in rabbits by the inoculations of streptococci obtained from various sources.

[1] *Journal of Infectious Diseases*, 1904, i, 714.

These, however, are more like the changes found in rheumatic fever. A remarkable instance of the production of "osteo-arthritic" lesions in a rabbit has been reported by Poynton and Paine,[1] who obtained in cultures, from the knee-joint of a man who had a chronic arthritis and died by accident, a diplococcus which injected into rabbits produced an arthritis characterized by destruction and formation of bone and cartilage. This differed from the arthritis produced by the diplococcus of rheumatic fever.

Pathology.—In a disease with so many manifestations it is difficult to give any description which will apply generally, and it is well to recognize that there may be all grades of change, from the slightest alteration to complete disorganization of the joint. Nor are the lesions always progressive; there is evidence that slight damage may be done which does not advance. As has been pointed out, there is usually no definite relationship between the etiological factor and the resulting change in arthritis; nor is there any regular association between the clinical picture and the pathological condition. Many causes may produce the same result, and one cause may produce various results.

In general, we may group the changes as follows:

1. *Effusion.*—This is not constant and shows no peculiar features. The fluid is generally somewhat turbid and contains cells which apparently have no special significance. Early in the course of the polyarticular form it may be distinctly hemorrhagic.

2. *Changes in the synovial membrane,* which are of an inflammatory nature and often hemorrhagic early in the attack.

3. *Changes in the capsule of the joint and surrounding tissue.*

4. *Cartilage.*—This may show erosion, atrophy, and ulceration. In certain cases there may be marked proliferation.

5. *Bone.*—This may show atrophy of slight grade, or in some cases this may be extreme. In other cases there is marked proliferation of bone, which may lead to extreme deformity. The formation of new bone may sometimes occur in the structures outside the joint, as in the ligaments.

Nichols[2] divides the lesions into (1) serous, (2) ulcerative, (3) ankylosing, (4) formative, and (5) fungus or villous. In the Cambridge report the principal changes as made out in the *x*-ray plates were: (1) Those limited to the soft tissues, (2) dislocation, (3) atrophy or destruction of cartilage, (4) atrophy and destruction of bone, (5) transparent areas, which look like punched-out holes in the plates and contain a gelatinous material; their significance is doubtful, (6) Bruce's nodes, which are small bony deposits, usually on the sides of the phalanges; they are probably not typical of any one condition, (7) deposits of new bone, (8) fibrous ankylosis, and (9) bony ankylosis.

It is convenient to discuss the alteration in the various forms of the disease, although the association of changes may be very marked. Two great forms of change may be recognized: first, those in the soft parts, and secondly, those in the cartilage and bones. In some cases one or other of these may predominate, but in many both will be found. It is frequently only by the *x*-ray plates that the second group may be recognized without opening the joint. Certain points may be noted. One is that suppuration never

[1] *Transactions of the Pathological Society of London,* 1902, liii, 221.
[2] *Keen's System of Surgery,* vol. ii.

occurs. Another is that the descriptions of changes found postmortem, years after the acute features have subsided, do not necessarily give any indication of what occurred early in the course. They are the remains of processes long since over. Again, secondary features are common, especially contractures and atrophy of the muscles. This latter is sometimes due largely to disuse, but again must be due to changes associated with the disease, as it comes on too rapidly to be due to disuse, and suggests some trophic disturbance. Again, there may be mechanical results, such as dislocation, which may be of very varying degree, and may occur with or without marked changes in the cartilage or bone.

In the peri-articular form there is often a considerable amount of *effusion* present, especially in the more acute attacks, which may persist for sometime. The fluid shows no peculiar features, although early in the course it may be distinctly hemorrhagic. Usually it is somewhat turbid and contains cells which have apparently no special significance. Cultures from the fluid have been negative in the experience of this clinic. The findings in an instance in which the knee-joint was opened may be quoted as characteristic. There were some slight hemorrhages in the neighborhood of the joint, which on being opened was found to contain 100 cc. of fluid. The synovial membrane was injected and showed papillary outgrowths of somewhat translucent connective tissue. The outer condyle of the femur showed erosion of the cartilage, the articular surface consisting of enamel-like bone; the corresponding surface of the tibia was the same. Certain areas were elevated, apparently due to overgrowth of cartilage. Sections of the synovial membrane showed on the surface an exudate of granular material and leukocytes. Below this were many bloodvessels and many leukocytes. Then came a layer of endothelial cells, which merged into the underlying fibroblasts.

Synovial Membrane.—This usually shows some thickening, which is more marked in the peri-articular form. If the joint is opened early in the course, the synovial membrane is usually swollen, injected, and redder than normal, the very vascular appearance giving a striking picture. The surface sometimes shows a velvet-like appearance, or is covered by a material not unlike granulation tissue. It may be covered with small processes of varying size or shape. The likeness of these to tubercles has led to that diagnosis being made. The synovial membrane may be thrown into folds. In some cases it becomes adherent to the adjoining cartilage, and where this occurs the cartilage is affected and usually destroyed. Histologically in the early stages there may be a marked hemorrhagic condition which is often well seen in pieces removed at operation. The capillaries are markedly distended, and there may be considerable extravasation into the tissues. This was so marked in one case known to the writer that a diagnosis of hæmophilic arthritis had been made. Nicholson in the Cambridge report describes two layers, the outer of which is more fibrous than the inner, and in it many fat cells may be seen. There is no marked collection of leukocytes, as is often seen in the inner layer. This is thinner, composed of delicate areolar tissue, and in some places resembles myxomatous tissue. Sometimes it contains large numbers of fat cells. One interesting feature is the presence of areas containing large numbers of mononuclear leukocytes, which are usually around the bloodvessels which show an obliterating endarteritis. There may be marked proliferation of this layer with the formation of villi. In some cases there may be an entire absence of the endothelial lining.

As the process advances there is usually thickening of the synovial membrane and an increase in the fibrous tissue. In some cases a certain amount of necrosis may occur. With proliferation of the synovial membrane the so-called villous arthritis may result, which in some cases is most marked. The villous processes are deep red in color and of very varying shape and size. They sometimes reach such a size that they distend the joint. As a rule, there is comparatively little effusion in these villous cases. Secondary changes may result; there may be calcareous deposits in the membrane itself or portions of the villi may become detached. These subsequently may undergo calcareous change. In some cases the synovial membrane becomes closely adherent to the surface of the cartilage, the destruction of which is most marked at this point. This is well seen in the case reported by Hale White.[1]

In the peri-articular form there is usually a good deal of thickening in the structures about the joints, and the ligaments may be involved. This can often be recognized on ordinary examination, but is especially well brought out by the *x*-ray plates. These may show the changes to be almost entirely outside the joint proper.

Cartilage.—The changes here are very varied in extent, and the slighter degrees may only be evident on opening the joint or in the *x*-ray plate. In the early stages the cartilage may be injected. The earliest change appears to be erosion, which in some cases seems to be determined by the proximity of the affected synovial membrane. The extent of this varies greatly, and the erosion may be of very slight extent, or in other cases it goes on until the whole cartilage has disappeared and the bone is exposed. Histologically there is fibrillation of the matrix, with disappearance of the cells. This may involve only the superficial layers and the structures below are normal. The process may advance until no normal cartilage remains. Apparently this is not always general, and there may be marked loss of cartilage in local areas; in other cases the whole surface shows thinning. The gross appearance of the cartilage is often striking. The surface is injected in parts, and often irregular, owing to the areas of erosion. In other cases the cartilage becomes liquefied and the corpuscles disappear with the formation of cysts filled with mucoid fluid. Nicholson describes the occurrence of necrosis in the cartilage with the formation of non-staining areas. This, however, he regards as being possibly due to gout.

In some cases there is apparently some formation of new tissue, in others there is considerable replacement of cartilage by fibrous tissue. The replacement of cartilage by bone is especially marked in the spine where the intervertebral cartilages may be entirely replaced. In the peripheral joints this rarely occurs. The result in any case is likely to be bony ankylosis.

Bones.—Here the changes vary with the form of the disease. In the peri-articular type there may be comparatively little change, although in severe cases there is considerable atrophy. This, however, is not distinctive and is similar to that seen sometimes with a fracture. If the changes in the cartilage result in its complete destruction the underlying bone becomes exposed and eburnated. If the process is very acute the bone is more vascular than normal and necrosis may result. In some cases the bone becomes rarefied and less dense. This can be seen in the *x*-ray plates and in pathological specimens.

[1] *Guy's Hospital Reports*, 1902, lvii, 25.

PLATE IX



Skiagram showing some thinning of the bones, marked destruction of the carpus, and alterations in the metacarpo-phalangeal and finger-joints.

PLATE X



Skiagram of Knee-joint, showing atrophy of the cartilage.

EXPLANATION OF PLATE XI.[1]

Fig. 1. Metacarpo-phalangeal joint.

Fig. 1*a*. Photograph of the same joint after maceration.

Fig. 2. Skiagram of a metacarpo-phalangeal joint, showing atrophy of cartilage and formation of new bone at the base of the first phalanx and head of metacarpal; a bony spur is also seen

Fig. 2*a*. Photograph of the same joint after maceration; the atrophy of cartilage, eburnation at head of bone, formation of new bone around joint, and a typical bony spur are well shown.

Fig. 3. Skiagram of first phalangeal joint, showing destruction of cartilage and fibrous ankylosis.

Fig. 3*a*. Photograph of same joint after maceration.

Fig. 4. Skiagram of the wrist, showing bony ankylosis and considerable atrophy of the bones forming the joint.

Fig. 4*a*. Photograph of the same specimen after maceration. This specimen on dissection showed complete bony ankylosis of the carpi at their articulation, and fibrous ankylosis of the ulnar, radius, and metacarpi.

Fig. 5. Skiagram from metacarpo-phalangeal joints, showing atrophy of cartilage and bone with fibrous ankylosis.

Fig. 5*a*. Photograph of macerated specimen of the same joint.

Fig. 6. Skiagram of the thumb, showing atrophy of bone and destruction of the cartilage of the metacarpo-phalangeal and phalangeal joints. Well-marked fibrous ankylosis is present.

Fig. 6*a*. Photograph of the same specimen after maceration.

EXPLANATION OF PLATE XII.

Fig. 1. Skiagram of a terminal phalangeal joint, showing atrophy of cartilage, early deposit of new bone in the ligament of joint, and a light area.

Fig. 1*a*. Photograph of the same joint after maceration. A cavity containing a deposit of urates is shown.

Fig. 2. Skiagram of the first phalangeal joint, showing atrophy of cartilage, formation of new bone around joint, and a well-marked projection from the shaft of the first phalanx.

Fig. 2*a*. Photograph of the same joint after maceration, showing a deposit of bone around joint and on the shaft of the first phalanx.

Fig. 3. Skiagram of first phalangeal joint, showing atrophy of cartilage and formation of new bone.

Fig. 3*a*. Photograph of the same joint after maceration.

Fig. 4. Skiagram of wrist, showing ankylosis.

Fig. 4*a*. Photograph of the same specimen after maceration. A longitudinal section has been made through the carpi and wrist-joint. The carpi are fused into a mass of light cancellous bone. The articulations of the carpi with the ulnar, radius, and metacarpi show fibrous ankylosis.

Fig. 5. Skiagram of metacarpo-phalangeal joint, showing atrophy of cartilage and the formation of bony spurs at the head of the metacarpal bone.

Fig. 5*a*. Photograph of the same joint after maceration. The bony spurs are well seen.

Fig. 6. Skiagram of a metacarpo-phalangeal joint from a case of arthritis deformans, showing atrophy of cartilage.

Fig. 6*a*. Skiagram of a corresponding joint from a case of chronic gout, showing similar changes.

[1] The writer wishes to acknowledge the kindness of the Cambridge Committee, especially T. S. P. Strangeways, and the Cambridge Press, in being given permission to reproduce these plates, which are taken from the *Bulletin of the Committee for the Study of Special Diseases*. 1907, vol. i, Nos. 3 to 9, Cambridge.

PLATE XI

FIG. 1

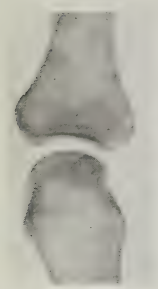


FIG. 1a

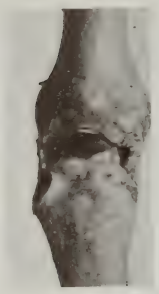


FIG. 2



FIG. 2a



FIG. 3



FIG. 3a

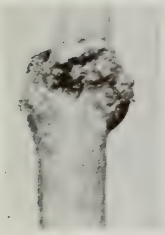


FIG. 4

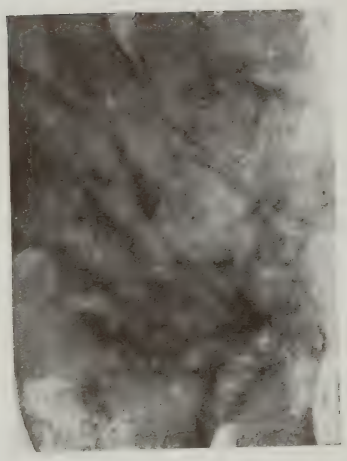


FIG. 4a



FIG. 5

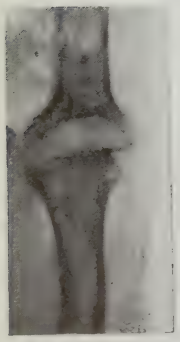


FIG. 5a



FIG. 6



FIG. 6a



PLATE XII

FIG. 1



FIG. 1a



FIG. 2

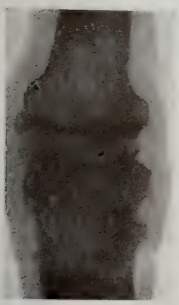


FIG. 2a

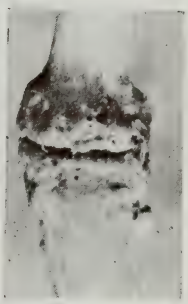


FIG. 3



FIG. 3a



FIG. 4

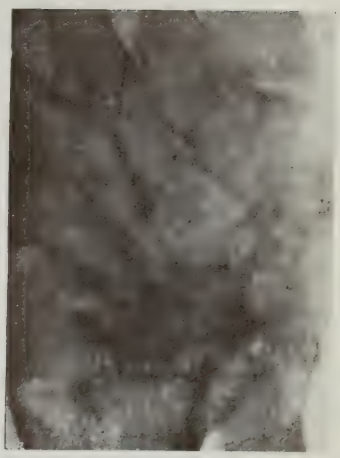


FIG. 4a



FIG. 5

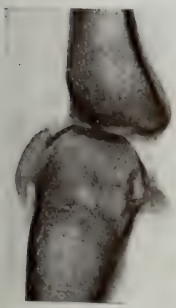


FIG. 5a

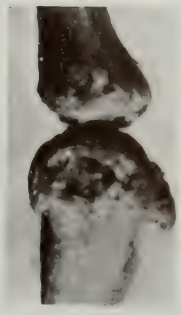


FIG. 6



FIG. 6a



In the so-called *atrophic* form the changes are of a different character. The most striking thing is the marked rarefaction of the bones throughout. With this usually goes destruction of the cartilage, so that as an end result (*e. g.*, in the wrist) there may be entire loss of the divisions between the carpal bones. It may be repeated that this change is entirely different from the atrophy which occurs secondarily to the more marked changes about the joint.

In the *hypertrophic* forms there is new bone formation, which may vary greatly in extent. The proliferation is most common at the edges of the articular cartilages, and the ossification may include parts of the adjoining fibrous or ligamentous tissue. This may result in bony outgrowths of varying size and shape. In some joints these projections may cause locking of the joint. In the knee-joint, bony outgrowths may be seen on the patella or at the edges of the femur or tibia. In the hip-joint these may be marked and surround the edge of the acetabulum with an irregular ring of bone. The so-called Heberden's nodes on the terminal phalangeal joints are formed of true bone. The same changes are sometimes marked about the metacarpophalangeal joints. In the spine the new formation of bone may replace the cartilages, but more frequently occurs in the spinal ligaments, and the anterior and lateral ligaments may be entirely replaced. In all of these irregularity of the deposits is the rule, and it is rare to find the deposits the same on both sides of the vertebræ. The deposit of bone has been compared to lava which has flowed down and solidified. Wright has well compared the appearance as sometimes being much like a "guttering" candle. This deposit of bone in the ligaments occurs especially in the spinal forms of the disease. It may be noted that spondylitis with deposit of new bone is common in animals, especially in horses.

Muscles.—Atrophy is the striking feature in the gross specimen, and this is generally found to be spread throughout the muscle. In some cases degeneration has been found, the muscle having a dead-leaf color, and there is proliferation of the nuclei with increase of the interstitial tissue. At times the changes are probably due to direct extension from the joint, in other cases it is suggested that they are due to trophic influences.

Nervous System.—No changes have been found which can be regarded as at all characteristic. In a few instances changes in the anterior horn of the cord have been noted. Vacuolation of the ganglion cells has been associated with altered staining reactions. In the peripheral nerves, neuritis has been found, but this is probably secondary. It is easy to appreciate how, for example, in arthritis of the spinal joints the inflammation may involve the nerve roots or in the hip the sciatic nerve. These changes are apparently always secondary.

Metabolism.—No very striking changes have been found. King,[1] in a study of the metabolism, found a mild acidosis, with an increase in the organic phosphates and a retention of calcium, magnesium, and phosphorus. The study of the urine did not suggest intestinal putrefaction. In some cases of the atrophic form the calcium output is much increased.

Symptoms.—While an exact classification is difficult, it seems best to discuss the clinical features under the various forms, always having in mind

[1] *Johns Hopkins Hospital Bulletin*, 1907, xviii, p. 274.

that there are not invariably clear-cut distinctions between them, and that it may be difficult to say exactly to which class a given patient belongs.

1. **Peri-articular Form.**—This is the most frequent form, and comprises the cases sometimes described as "rheumatoid" arthritis. The changes are most marked in the synovial membrane and peri-articular tissues. The cartilage is also affected in many cases, but the damage is rarely extreme; whatever change occurs in the bone or cartilage is apparently secondary. In this group we find every grade of change, from that seen in the patient who has a light attack, resulting in very little thickening about the joint, to the patient who has changes so marked that he is a miserable cripple, perhaps unable to feed himself. There were about 240 cases typically of this form; there were others which were predominantly of this group, but showed features of the hypertrophic form as well. The females outnumbered the males in about the proportion of 3 to 2.

Onset.—This is usually in one of two ways, acute in one or many joints or gradual in one joint, others being slowly involved subsequently. A point deserving of marked emphasis is the marked suddenness of onset in some cases. It is not unusual for patients to be able to state the exact date of onset; some can even give almost the hour. Thus, in one patient the onset was with severe pain while he was walking on the street. The pain was so intense that he was unable to walk and had to be carried home. Some descriptions of the disease lead one to suppose that the onset is always gradual, but this is not correct, and of the cases in this series which were regarded as belonging to this form the onset was acute in about 40 per cent. The sudden onset is usually with an acute arthritis of many joints, which are red and swollen. Occasionally one joint is suddenly involved acutely for a day or two and then others follow. There is rarely any marked constitutional disturbance or chill. One feature sometimes seen is the sudden disability; thus, in one patient the process began in the knees, while he was walking home, and the pain was so severe that he was compelled to sit down for a time, ultimately reaching his house after resting several times.

The gradual onset may be in one or several joints. It is often found that one joint becomes swollen or painful, perhaps never red, and after some weeks, or possibly months, another follows. As a rule, the gradual onset is of more serious omen than the acute one, which often runs its course more rapidly.

Joint First Involved.—Leaving out the cases in which the onset is with the simultaneous involvement of many joints, many more have the first symptoms in one of the joints of the leg than in the arm. It has been said that the disease is prone to attack first the joints which are most used. However this may be, the statement so often repeated that the disease usually begins in the joints of hands is certainly not correct. In this series the figures of the first joint affected, when this was definitely known, are as follows: Many joints, 22 per cent.; neck, 3 per cent.; shoulder, 12 per cent.; wrist, 8 per cent.; hand, including the thumb, 10 per cent.; hip, 7 per cent.; knee, 19 per cent.; ankle, 3 per cent.; foot, 13 per cent. Certain combinations of joints comprised the remainder. The onset was more often in the joints of the lower than in those of the upper extremity.

Character of the Attacks.—As in the mode of onset, so in the course, two principal forms stand out, the one with acute attacks of polyarthritis, the other with a slow, chronic, more or less progressive course. There are many

combinations and varieties. Thus, there may be repeated acute attacks at intervals, the patient being comparatively well in the meantime, or after the acute attack there may be a slow, gradual progress, or during the course of the chronic form there may be intercurrent acute attacks. However, it aids our clinical knowledge to keep these two classes in mind, recognizing that there are some which cannot be placed in either. In this series about one-third might be classed as acute, one-half as chronic, and the remainder with features of both.

The Acute Form.—It may be said that in many ways this group is much like rheumatic fever in its manifestations. The onset is often sudden, with the involvement of many joints. These are red, swollen, painful, and tender to the touch. There is often effusion in the larger joints. Certain joints not often involved in rheumatic fever may be affected, such as those of the cervical vertebræ, the temporomaxillary and sternoclavicular joints. One point is important—when a joint is once attacked it rarely clears immediately and the involvement is usually for the duration of the attack. Again, as the acute features subside, the joint usually shows some permanent change which may be slight, but it is there. Thus, the finger-joints show slight increase in size or the capsule of the knee-joint is thickened.

Certain general features may be noted. The temperature, as a rule, is not very high, being generally about 101° or 102° F. Occasionally higher figures are seen, sometimes 103° or 104°, but this is rarely for longer than a few days. After a time the temperature often drops to 100° or 101°, and may run along about these figures for some time. Chills and sweating are both uncommon. The pulse generally shows a rate which is comparatively high, and this persists after the temperature has fallen. In a number of cases there is definite *enlargement of the spleen*, which may be made out by palpation, or the area of dulness is increased. *Glandular enlargement* is almost always present. This is usually general, with the glands in relation to the affected joints showing the most marked increase in size. As a rule, the administration of the salicylate preparations has but little result. The persistence of the arthritis is one of the most striking features.

The Chronic Form.—In this the onset is usually gradual, frequently in one joint which swells gradually and is painful. There is rarely any redness, and effusion in the larger joints is not common. In some cases there may be complaint of pain in one joint for weeks before any change can be made out on examination. Other joints are progressively attacked, and it may be a year before there is general arthritis. In other cases one or two joints may be affected for a time, and then with a somewhat acute attack several joints are involved simultaneously. Again, the process may be rather subacute and gradually assume the slow, progressive type. The *temperature*, as a rule, is not high, often running for weeks from 99.5° to 101°. It is fairly constant and may never touch normal. The pulse is high, often 110 to 120 or more, and remains persistently so. Enlargement of the *spleen* is not so often found as in the more acute forms. The lymph glands in relation to the affected joints usually show enlargement.

In seeking for an explanation of these various manifestations it is tempting, in the line of a probable infective cause, to consider that the acute type shows a more marked response and more active resistance to the infective agent and its toxins. There is little question but that the outlook, especially for the end results in the joints, is much better in the acute forms.

The special features may be taken up for this whole group in some detail.

Pain.—This shows much variation, as in some patients there is comparatively little so long as the joint is at rest; after the subsidence of acute features, pain usually comes only on movement either active or passive. In other patients severe pain is a constant feature, and may continue long after all acute features have subsided. The amount of pain and degree of arthritis bear no relationship to each other—in fact, some of the patients who have the most severe pain have very slight joint changes. There are certain situations in which the complaint of persistent pain is common. One of these is about the heel; there may be no special tenderness on pressure, yet every attempt at walking causes so much pain that the patients have to remain at rest. The *x*-ray plates show no bony changes to account for it. Pain in the wrist-joint and hand is sometimes very severe and constant. There may be severe pain from an associated neuritis, as occurs especially with involvement of the shoulder- or hip-joint. The pain may follow the distribution of a nerve, and be markedly increased by pressure over it. In the arthritis of the spinal joints the pain may be severe.

Arthritis.—In considering this it is convenient to discuss the joints separately, as the features differ considerably. *Vertebræ:* Quite apart from the condition termed spondylitis deformans in this article, we find the joints of the spine not infrequently involved along with the peripheral joints. In addition, as will be discussed later, the manifestations of spondylitis deformans may be found with a general polyarthritis, but in this there are definite changes in the spine. It is important to realize that the joints of the vertebræ may be involved in a general polyarthritis, and apparently no permanent change of any degree be left—at any rate, none which can be demonstrated. There is an acute arthritis which subsides without causing structural change. The most frequent seat of involvement is the joints of the cervical vertebræ, as occurred in fifty-one cases. There is complaint of pain, especially on movement; the head may be held more or less fixed, sometimes to one side, as the involvement is not necessarily symmetrical. Pain on movement may be very marked, sometimes more on movement in one direction than in another, and it may be marked on pressure; sometimes distinct grating on movement may be heard by the patient, and it is often audible to the physician. There is rarely any permanent fixation of the neck, as after a variable period the process clears up and movements are restored. Tenderness on deep pressure may persist for sometime longer.

In addition there may be a similar process elsewhere in the spine (thirteen cases), with or without the cervical vertebræ being involved. With an arthritis of the peripheral joints there may be the complaint of severe pain in one part of the spine. This is tender on pressure, the spinal muscles are rigid, and movements cause severe suffering. The duration is often for several weeks. It is rare in these attacks to find signs suggestive of pressure on the nerve roots or marked muscular atrophy. It is important to realize that this may clear completely without any evidence of permanent change, the *x*-ray plates not showing anything abnormal. If the point is looked into it is not rare to get a history of these attacks, and a number of patients with definite bony changes in the spine give a history of previous attacks of this kind, after which there was apparently complete recovery before the permanent condition was present.

Temporomaxillary Joint.—This is involved much more often in arthritis deformans than in any other form of arthritis, so that its involvement is an important point in the diagnosis. It was affected in forty-three cases of this series. The patient complains of pain and difficulty in moving the jaw. The extent of involvement varies greatly. There may be little more than the complaint of pain, or the patient may be unable to open his mouth. Not infrequently the joint on one side only is involved, or one may be much more affected than the other. The process is often present for a short time only. Fortunately the amount of permanent change is usually slight, and it is rare to have complete ankylosis. For a time the patient may be able to open the jaws very slightly, and occasionally teeth have to be removed in order that the patient may be fed, but this was rare in this series.

Sternoclavicular Joint.—This was involved in fourteen instances. There is pain, aggravated by any movement of the clavicle, and slight swelling. In rare cases the swelling may be quite marked. As a rule, the arthritis clears up completely without any troublesome changes.

Shoulder-joint.—This is frequently involved, as in 126 cases of this series, of which 91 had both shoulders, 22 the right only, and 13 the left only involved. In the acute stages there is pain and limitation of motion, especially in elevating the arm above the head and in abduction. There is often tenderness on pressure over the joint, and on anything more than the slightest movement. There is rarely marked effusion; the thickened capsule can often be felt. More or less associated neuritis is not uncommon, the pain being described as running down the arm or up the neck toward the head. As the acute features subside there is often considerable stiffness, crepitus, and thickening of the capsule, with diminished motion. If the process be long continued there is generally marked atrophy of the muscles of the shoulder girdle. After any attack of moderate severity there is almost sure to be some disability left behind.

Elbow-joint.—There was involvement of this joint in 76 cases, both elbows being involved in 52, the right in 9, and the left in 13 cases. In the acute attacks the elbow is generally held in a somewhat flexed position, movement is often considerably restricted, and the swelling may extend for some distance above and below the joint. This is often more marked about the elbow than in other joints. Movements other than those of flexion and extension are often considerably diminished. Pain is rarely extreme, but there may be considerable tenderness on pressure. In later stages the extension is often limited, but there is rarely a marked degree of thickening left about the joint.

Wrist-joints.—These were involved in 98 cases, both wrists in 79, the right in 11, and the left in 8 cases. The changes in these joints are generally very characteristic. As a rule, there is a good deal of swelling, which may extend above and below the joint, so that the ordinary contour is entirely altered. The swelling frequently has a soft boggy feeling, and there is commonly decidedly less pain than in other joints in proportion to the amount of change. Crepitus is often obtained fairly early. In the subsequent stages the swelling usually subsides, but there is often very definite thickening about the joint, with some restriction of motion. In regard to the early stages of the disease, it is interesting to note, as Spender pointed out, that there may be complaint of pain in the wrist-joint, especially on the ulnar side, sometimes associated with weakness, so that there is a tendency to drop objects held in the hand before there are any acute signs of arthritis.

Hands.—It is worthy of mention that the hands are not always involved, as some descriptions would lead one to expect. The changes in the metacarpophalangeal joints are often very striking. There is generally some swelling, redness, and tenderness, especially on motion. This leaves behind some thickening and disability. The degree of involvement in these joints is very variable, and only one knuckle may be involved or all of them on both hands. The condition after the acute features have subsided is generally very characteristic. In some cases there may be subluxation of the joints; one form of change, the ulnar deflection, being quite common. This may come on very rapidly in acute cases—thus, in one patient it was marked within one month of an acute onset. A striking feature is atrophy of the interossei muscles, which is frequently found. In occasional instances this may be present without any involvement of the joints of the wrist or hand.

Fingers.—These are involved in a considerable number of the cases (106 without any joints of the hands), and the changes, as a rule, are very characteristic. In the earlier stages there is usually some swelling, which is often most marked at the first interphalangeal joint. The swelling can be made out to be definitely in structures about the joint proper, and the *x*-ray plate may show the same. The fingers are very often held slightly flexed and full extension may be difficult. With involvement of the fingers and the knuckles it may be impossible for the patient to make a fist. As the acute features subside a very characteristic picture is usually left behind, the thickening about the joint giving the so-called pod-shaped or fusiform finger. Subsequently there may be quite marked changes in the joints, especially in the way of partial dislocations. A common picture is flexion of the first phalanx, with hyperextension of the terminal ones; but all the joints may be partially flexed, or only the terminal one show hyperextension. Lateral deflection is quite common, especially in the terminal joint. Hyperextension of the terminal phalanges may come on very rapidly, as in one patient with acute features in whom this was marked within three weeks of the onset. The thumb-joints are not uncommonly involved.

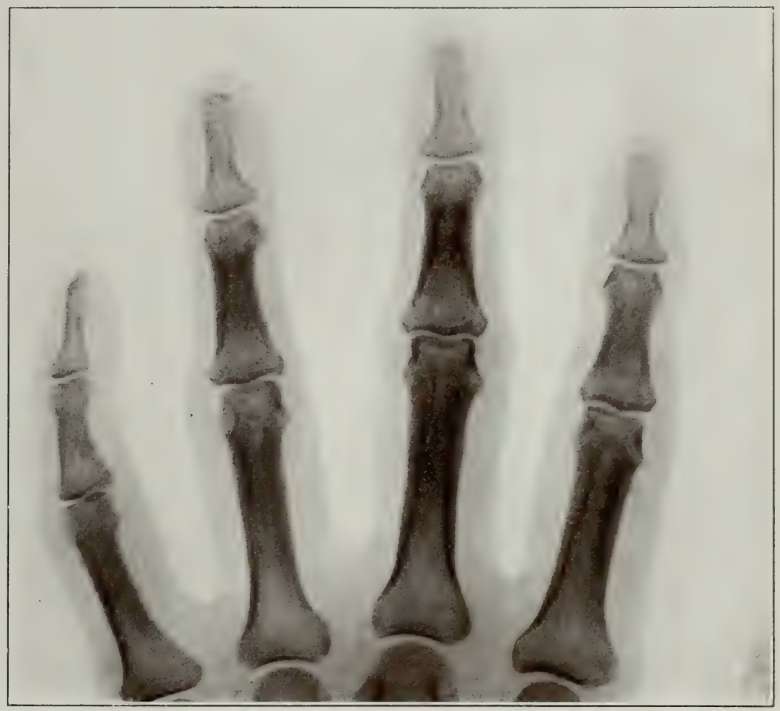
Sacro-iliac Joint.—Apparently this is not often involved in this form of the disease, and it is often difficult to decide whether the arthritis is of this form or hypertrophic.

Hip-joints.—As a rule, the changes in this form of the disease are not marked; these joints were involved in 89 cases, both hip-joints in 65, the right in 14, and the left in 10 cases. The condition is usually not as marked as in the hypertrophic form, or in the variety associated with spondylitis. During an acute attack of polyarthritis there is complaint of pain in the hip-joint and some pain on movement. On examination little may be made out except slight restriction of movement, especially on abduction and internal rotation. If only one joint be involved the patient may walk so as to favor that side. As a rule, permanent damage of any extent does not result, although at times there may be some fixation with the thigh flexed.

Knee-joints.—This is the single joint most frequently affected, as occurred in 236 cases, both knees being involved in 202, the right only in 19, and the left in 15 cases. The small relative number with involvement of one side only is a contrast to the findings in other joints. In the acute stage the joint is often markedly swollen, red, and tender. Effusion often occurs, and the patella may "float." On palpation there may be considerable tenderness, especially on the inner side, and sometimes over the inner part of the head of

PLATE XIII

FIG. 1



Skiagram showing the swelling about the first phalangeal joints, with little change in the articulating surfaces.

FIG. 2



Hands showing marked late deformity.

the tibia. Tenderness may also be marked in the popliteal space. The joint is commonly held somewhat flexed. As the effusion is absorbed the thickened capsule can usually be felt best on the inner aspect of the joint. If there is much change about the joint, some flexion usually occurs with contraction of the tendons, which later may go on to subluxation. In some very acute cases, and in some chronic ones, in which there is a good deal of muscular atrophy, marked enlargement of the bones may be suggested. This, however, is apparent and not real, being suggested by the atrophy above and below the joint.

Ankle-joints.—These were involved in 130 cases, both in 101, the right in 17, and the left in 13 cases. They often show much the same features as the wrists, considerable puffy swelling extending above and below the joints. There may be considerable stiffness and limitation of motion, which, however, is usually not permanent. The bones of the feet may be involved with the ankle-joint or separately. The joints of the feet were involved in 53 cases.

Toes.—The toes were involved in 40 cases, there being a striking difference between the number showing involvement of the fingers and toes. The changes are much like those seen in the fingers, but are usually less marked. In some cases there is the complaint of persistent pain in one or more toe-joints without any evidence of active arthritis. In some instances ankylosis occurs in the great toe-joint.

General features of the arthritis. (*a*) *Symmetry of the Involvement.*—Much stress was laid on this by the earlier writers, but it is by no means the rule when the figures as to the frequency of the involvement are studied. Thus, in 35 among 126 cases of arthritis of the shoulder the process was unilateral, in 22 of 76 cases of the elbow, and in 24 of 89 cases of the hip. In certain instances the disease may involve one side of the body only, or all the joints of one extremity. It is rare for a single pair of joints, as the knees, to be involved alone.

(*b*) *Distribution of the Lesions.*—This is very variable, and every combination occurs. In the total number of joints involved the arms exceed the legs, but only by a small amount. If the larger joints are considered, the contrary is the case, and the greater number is in the legs. The frequency with which the hands are involved accounts for the larger total for the upper extremity.

(*c*) *Variability in the Changes.*—This is seen especially in the acute attacks, which involve many joints. The majority may recover without much change, the brunt of the attack falling on one joint. Both hands may seem to be equally involved at first, and yet one regains almost complete function, the other showing marked change. Sometimes there seems to be some influence from occupation and special strain on particular joints, as, for example, in those who sew or use one hand more than the other in their work.

Muscular Atrophy.—This is commonly present to some extent, but varies greatly in different patients, both in its extent and rapidity of development. In some patients, especially in acute attacks, atrophy advances so quickly that some trophic influence seems necessary to account for it. This is usually most marked in the hands, the interossei muscles showing very rapid change. In other cases the progress is slow and disuse may seem to be quite a sufficient explanation. However, there is usually more than this necessary to account for it. In some patients with repeated acute attacks there may be little change with the first one or two, but each subsequent attack shows more

change. About the shoulder-joint the atrophy is sometimes well shown. An interesting point is the occurrence of *muscular twitching*, sometimes seen as a fine fibrillary tremor, which is very marked in some patients.

Temperature.—Two points stand out in the consideration of this: first, that the fever often shows an elevation much less than might be expected from the degree of arthritis; and second, that it may persist for a long period very slightly above normal. The figures for patients who were under observation long enough to obtain satisfactory records (the patients in whom all acute features had subsided are not considered) showed that in the largest number the temperature averaged from 99° to 100° or 101°. Although at times it was higher, yet this rarely persisted, and many patients go for weeks with a temperature between 99° and 100°. This suggests a chronic low-grade infection. In some cases a rise to higher figures occurs with a complication, such as pleurisy or pericarditis. In a few patients no such explanation could be found. In one instance with a severe shaking chill the temperature rose to 104°; no cause was found, malarial fever being excluded. The persistence of slight fever with a relatively high pulse rate is often an important point in diagnosis. It must also be noted that with an acute polyarthritis the temperature sometimes remains practically normal. There were several instances of this.

Circulatory System.—Among 350 cases there was evidence of definite valvular diseases in 25 instances. The lesion was mitral insufficiency in 9 cases, mitral stenosis in 3, combined mitral stenosis and insufficiency in 3, aortic insufficiency in 5, aortic and mitral insufficiency in 3, and aortic insufficiency with mitral stenosis and insufficiency in 2. In about one-quarter of these there was arteriosclerosis, so that the lesions might be regarded as sclerotic; in the remainder they suggested an endocarditis. In 19 cases there was an apical systolic murmur which was not definitely proved to be due to organic valvular disease. In some others there were signs of myocarditis.

Pericarditis occurred in three cases while under observation and during the course of the acute arthritis. Effusion followed in two; in one of these tapping was done repeatedly and the fluid injected into guinea-pigs, but with negative results. Phlebitis occurred in one patient; it was associated with an attack of lobar pneumonia.

Pulse.—This shows an increase in the rate in the majority of cases. In about two-thirds of the cases the rate was over 90. The most frequent range is between 90 and 110, only a few patients having a persistent rate above 120. This increase in rate is true not only of the acute periods, but frequently persists after these have passed, and is also seen in the slowly advancing forms. When fever is present the pulse rate is usually elevated quite out of proportion to the temperature. An explanation of this is not easy to give. In a few instances there were definite evidences of myocarditis, occasionally with dilatation, but this is by no means the rule. The blood pressure shows no special departure from the normal.

Respiratory Tract.—Bronchitis was present in few instances, and in some it was suggested that the infection which caused it might stand in some relationship to the arthritis. Lobar pneumonia occurred in two patients during an acute arthritis, in one being associated with a marked exacerbation of the joint condition, which rapidly subsided after the pneumonia was over. The greatest interest, however, is attached to the occurrence of *acute pleurisy* with the arthritis. This occurred in six cases, one of which

was tuberculous and associated with tuberculous disease of the lung. The others were not tuberculous, as was shown by the negative reaction to tuberculin given after the acute features had subsided and the temperature had become normal. In two patients the pleurisy was associated with an acute pericarditis. The importance of this as suggesting some infectious process is evident.

Glandular Enlargement.—Among 176 cases in which this point was specially noted, general glandular enlargement was found in 99 and enlargement only of certain groups of glands in relation to the affected joints in 44. The degree of enlargement varies greatly, those glands which are in relation to the more acutely affected joints showing the greatest involvement. Thus, the joints of one arm may be involved and those of the other be normal, the glandular enlargement being on one side only, or general glandular enlargement is present, which is more marked on the affected side. The enlargement may persist for some time after the acute arthritic features have subsided. Occasionally the enlarged glands are slightly tender. Histological examination shows only a hyperplasia. In some cases the enlargement is persistent. Thus, in one patient with the onset eight years before and in whom five years had elapsed since any acute features, there was marked increase in the size of all the palpable glands. This he had noted himself as having come on soon after the onset of the arthritis. His blood was perfectly normal and no other cause for enlargement could be found.

Spleen.—Among 166 cases with notes as to the size of the spleen, it was found that there was enlargement in 38, in 30 the spleen was palpable, and in 8 the area of dulness was definitely increased. In practically all the cases with splenic enlargement, there was general glandular enlargement. The cases of the so-called Still's disease are included here and will be referred to later. It may be said in a general way that enlargement of the spleen was relatively more common among the younger patients, although it is not confined to them. It is also more frequently found in acute than in chronic attacks. This and the glandular involvement seem to support the idea of some infectious process.

Subcutaneous Fibroid Nodules.—These are very interesting structures, which perhaps might be better termed "subcutaneous nodules," as they are not always fibroid in character. Long regarded as diagnostic of rheumatism, this view can no longer be held, as they may occur in some cases without any evidence of arthritis of any kind. However, it can be said in the majority of cases they are associated with arthritis, and in the experience of the writer this has been rheumatic fever in children and arthritis deformans in adults. In this clinic we have been much interested in them, especially since the paper by Futcher,[1] and they have been searched for, an important point when one is quoting figures as to their frequency. In this series they were found in 12 patients (3.4 per cent.), all being adults. All the cases found in rheumatic fever were in children. In the patients with acute rheumatic fever in this clinic, subcutaneous nodules were found in 1.5 per cent., but, of course, only a comparatively small proportion of the patients admitted are children.

They are generally found about the elbow or wrist, sometimes on a finger, are rather hard, round bodies, between the size of a grain of wheat and a pea, quite frequently movable, and sometimes tender. Their duration is

[1] *Johns Hopkins Hospital Bulletin*, 1895, vi, 133.

very variable and they may disappear in a few days or persist for weeks. Occasionally patients volunteer the statement that they have been noted to appear, disappear, and re-appear. They do not seem to be associated with any severe type of the disease or with any special joint features. An interesting monograph on them has been written by Hawthorne.[1]

Urine.—This showed no features of moment. In about 20 per cent. of the cases albumin was found, and in rather more than half of these casts were present. Diabetes co-existed in two patients. Estimations of the amount of uric acid were made in a number of cases, but showed no constant departure from normal. Helen Baldwin[2] has described the occurrence of organic acids in the urine, suggesting perverted metabolism and intestinal putrefaction.

Blood.—It may be said that the examination of the blood yields little of importance. The majority of patients have a pale, sallow look, and often suggest a degree of anæmia which is not confirmed by the blood count. The average percentage of hæmoglobin in 132 cases was 77; the average red count in 125 cases was 4,763,000, and the average leukocyte count in 132 cases was 8800 per cmm. Leukocyte counts taken during the occurrence of a complication, such as pneumonia, are not included. The leukocyte count in 36 cases was over 10,000, and in 10 cases below 5000 per cmm. It is surprising to find that frequently during an acute polyarthritis the white corpuscles are not increased. The average differential count of the leukocytes in 25 cases showed: Polymorphonuclears 78 per cent., small mononuclears 13.8 per cent., large mononuclears and transitionals 6 per cent., eosinophiles 1.7 per cent., and other cells 0.5 per cent. In the case of complications, such as pleurisy, there was a marked polynuclear leukocytosis, which showed no unusual features.

It may be said that the blood condition was practically the same in all the forms of the disease. The patient with acute arthritis involving many of the peripheral joints showed practically the same blood condition as the one with the spine alone involved. These findings are in agreement with those of Erving,[3] who made a study of the subject.

Skin.—One of the most striking phenomena is the presence of pigmentation, which is especially apt to occur on the face, neck, arms, and hands. It may be fairly general over the face and neck or occur in irregular areas; on the hands and arms it more often is seen in smaller, more irregular areas. In some patients there are many small pigmented areas, much like freckles. As a rule, the pigmentation is associated with acute general features, and as these subside the discoloration lessens, sometimes, however, leaving some "staining." In this series marked pigmentation was noted in 28 cases, about equally divided between the sexes. It may occur almost at any age, the youngest in this series being nineteen years and the oldest seventy-eight years. It may be said that there is nothing distinctive about this pigmentation; it occurs with many other diseases.

In some cases, especially in those with marked and rapid muscular atrophy, the skin has a curious glossy appearance. This is usually in the hands or feet, but may extend to the arms or legs. In some patients the hands and feet may be very blue. Profuse sweating of the hands and feet is common,

[1] *Rheumatism, Rheumatoid Arthritis, and Subcutaneous Nodules,* London, 1900, J. & A. Churchill.

[2] *American Journal of the Medical Sciences,* 1904, cxxviii, 1038.

[3] *American Medicine,* 1903, vi, 440.

and may be a source of great discomfort to the patient. This may persist long after acute features have disappeared. In the more chronic forms the skin is often harsh and dry. There may be disturbance of sensation, especially as regards pain, and this may be found to differ on the two sides if the arthritis is asymmetrical. R. L. Jones[1] notes that there may be areas showing sensory changes and sometimes local sweating. Complaint of numbness or tingling, sometimes of severe burning sensations, is not uncommon. Erythema or urticaria may occur sometimes. Herpes of the lips has been seen occasionally.

Reflexes.—These very commonly show some alteration, but the findings are by no means constant. The deep reflexes are, as a rule, markedly increased, but may be normal or decreased, although they are rarely absent. In many instances they vary in relation to the joint involvement, and may be greatly different on the two sides of the body or in one extremity. They are usually increased on the diseased side. In 66 cases the following conditions were found: the deep reflexes of the arm were increased in 34, and diminished in 3; increased on one side and normal or diminished on the other in two. The knee-jerks may show a most marked increase. They were increased in 43, diminished in 7, and increased on one side while normal or diminished on the other in 4. If there is involvement of the temporomaxillary joint, the jaw-jerk is generally increased. The superficial reflexes are very variable, and may be much increased or greatly diminished. The cremasteric reflex was very variable, sometimes being markedly increased, in others normal, diminished, or absent. Ankle clonus was present in 8 cases on both sides and in one case on one side only. Patellar clonus was obtained in 2, and clonus in the arms in one case. Plantar stimulation in one patient gave a normal response on one side and none on the other. In a few cases there was an extensor response. In many cases the reflexes were especially exaggerated when there was marked muscular atrophy. R. L. Jones has pointed out that there is often a correlation between the affected joints and certain reflexes. Thus if the middle and ring fingers alone are involved, the flexor tendons give a more marked response to tapping than the extensors. The reverse is the case if the thumb and index finger be involved. He points out that there is often marked agreement in the gluteal and plantar reactions. The increase in myotatic variability he regards as of some aid in prognosis as it appears early, and if persistent suggests that the process is still active. Its disappearance is of good omen. Jones lays stress on the association of conditions (*e. g.*, of the plantar and gluteal reflexes), as suggesting some affection of certain spinal segments. In some cases there may be considerable uncertainty of movement, which usually does not amount to tremor.

Œdema of the feet and legs sometimes occurs, apart from any renal or circulatory lesion. It may be seen in acute attacks or more often in patients with marked lesions in the joints of the legs, especially if there is flexion of the knees with immobility. It is also seen in the patients who are unable to get about and sit all day in a chair.

Features of the Disease in Children.—There is much uncertainty as to the occurrence of chronic arthritis in early life, and unanimity of opinion has not been reached any more than in regard to the anæmias of early life. As

[1] *The Lancet*, 1902, ii, 1746.

Garrod[1] points out, chronic arthritis in childhood is of various kinds. Some rare cases suggest the hypertrophic or osteo-arthritic type which may be the same as that seen in adults. Again, bony changes may occur after hæmophilic arthritis, as shown by Bowlby. Garrod also refers to rare cases in which chronic arthritis follows acute rheumatic fever, a condition which the writer must confess he has never been able to recognize. Then certain cases of tuberculous polyarthritis in children present curious features, and syphilitic arthritis in childhood may be chronic. However, all these are rare conditions and not so common as the form of polyarthritis in childhood, which has been termed "Still's disease." Special attention has been drawn to this by G. F. Still,[2] of London. There are three prominent features: a chronic arthritis characterized by enlargement of the joints, marked general glandular enlargement, and enlargement of the spleen. While different diseases may be included under the term, as has been suggested, yet the writer is of the opinion, judging from the patients studied in this clinic, that it is not a distinct entity but arthritis deformans occurring in childhood. All the cases in this series have been of the peri-articular type; none have been recognized as of the hypertrophic or osteo-arthritic type, although one of the hypertrophic form in this series began at the age of fourteen years. There seems no reason why the hypertrophic form might not occur in earlier years. On the view that these cases are manifestations of arthritis deformans in childhood, they are included in the general statistics given before, but their special features will be considered here.

Age.—At what age should we draw the line? From the experience of this series it is impossible to say arbitrarily what patients should be put in the class of "Still's disease." There was a series from four years of age up to eighteen with a gradual lessening of the typical picture in the older patients. Still states that the onset of the condition described by him is before the second dentition, and yet in this series one boy, aged eleven years, showed a perfectly typical picture of it. Practically the same condition may be seen in still older children, and, as has been pointed out, enlargement of the spleen and lymph glands is by no means uncommon in later years. In childhood these are undoubtedly likely to be more marked and persistent, but hardly afford ground for separating a distinct entity.

In these cases in childhood the arthritis comes on insidiously and advances slowly. It is of the peri-articular type, the thickening is usually marked, and there may be some limitation of motion. There may be marked muscular atrophy and wasting. Enlargement of the glands is marked; they are discrete and rather hard. Their size often stands in direct relation to the degree of arthritis in the neighboring joints. The spleen is usually felt below the costal margin and is hard, its size varying with the arthritis. The pathological anatomy is not different from that found in the disease at an older age.

The condition is chronic and in the majority of reported cases has advanced until the patient is completely crippled. This has not been the experience of this series. One patient left somewhat improved, a second left the hospital with the disease apparently arrested and the condition of the joints improving. When seen a year later there had been no return of acute symptoms,

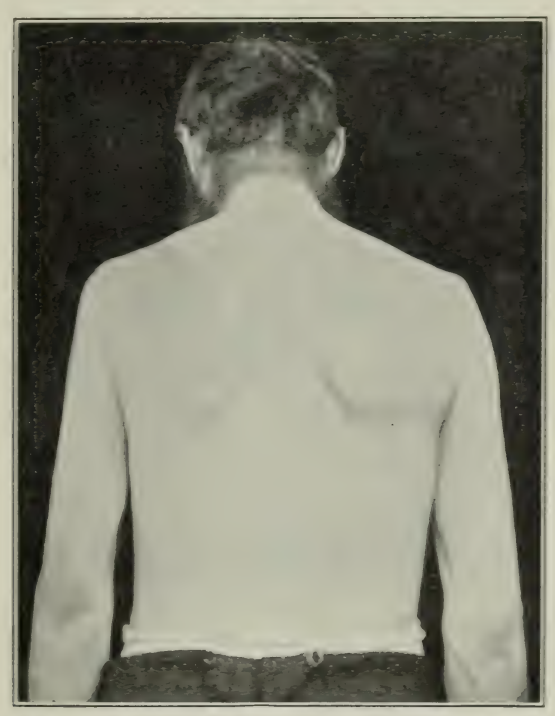
[1] *A System of Medicine* (Allbutt and Rolleston), revised edition, 1907, vol. iii.

[2] Medico-Chirurgical Transactions, London, 1897, lxxx, 47. *A System of Medicine* (Allbutt), London, 1897, iii, 102.

the child had grown, was able to get about well and showed only some slight thickening about the joints. The third patient showed considerable improvement and was able to get about. The fourth, aged eleven years, remained in much the same state.

The Peri-articular Form in Advanced Life.—While the view is sometimes expressed that in elderly patients the disease is likely to be more chronic, yet this is not by any means always the case. The first attack may be a very acute one, as in a patient, aged seventy years, who had never suffered from

FIG. 8



An example of the so-called monarticular form involving the right shoulder-joint. This patient had slight changes in two fingers, the result of an attack some years before.

any arthritis previously. Her attack began suddenly, involved many joints, and resulted in considerable permanent change within three months, after which the process subsided. In other instances there may have been a rather chronic progress, or perhaps slight attacks years before, and later in life the first acute attack appears. There is one form occurring usually in stout elderly women which is worthy of note. In such patients the process may be rather chronic, and perhaps has caused slight changes in the small joints, but the brunt of the attack falls on the knee-joints. These are painful, rather stiff, and apt to "give way" without warning, so that the patients

are afraid to walk without some support. On palpation there may be only slight tenderness and the thickened capsule may be felt. Painter[1] aptly applies the term "knee-sprung" to them. He regards them as being of the hypertrophic type, but some are undoubtedly peri-articular.

The So-called "Monarticular" Forms.—This is not a good term, but has been used to describe a form of arthritis usually seen in advanced life, in which one large joint is especially involved. It is a misnomer in the majority of cases, for, if careful examination be made, it is generally found that there is slight involvement elsewhere. The joints most frequently involved are the shoulder and hip. The changes in the shoulder-joint are usually of the peri-articular form, while those in the hip-joint are of the hypertrophic form. The process sometimes attacks the arm which is especially used (*e. g.*, the right arm in a carpenter). The principal symptoms are severe pain, marked disability, especially for certain movements, such as raising the arm and putting it behind the back, and extreme muscular atrophy, often involving the whole shoulder girdle (Fig. 8). Two other conditions have to be kept in mind, one is associated with it and the arthritis is often unrecognized, the other it resembles and may not be suspected. The first is neuritis, which true enough is present, but secondary to the arthritis, and the other is sub-deltoid bursitis.

As will be pointed out later, one large joint (shoulder or hip) may be involved with the whole spine (spondylitis deformans), but in these cases no special peculiarity is manifested in the peripheral joint, except perhaps marked muscular wasting.

2. **Atrophic Form.**[1]—This is much the least frequent in occurrence, which is fortunate, as it is in many ways the most serious as regards outlook. The most marked anatomical change consists in the atrophy of the bone, which may be very advanced. There is marked loss of the calcium salts. With this there may be extreme disorganization of the joint, which, as regards function, is practically destroyed. The progress in some cases is extremely rapid, and they might almost be described as fulminating.

This form usually occurs in young adults, and more often in females than in males. It usually begins about the wrist and hand. The symptoms do not differ very greatly from those seen in the peri-articular form, except that muscular atrophy and disorganization of the joints are more marked. The deformity is often greatly due to dislocation, which is favored by the marked loss of cartilage. Ankylosis, which is usually fibrous, may follow. The hand and wrist have a characteristic appearance. The patient may have difficulty in even lifting the hand or in performing any of the ordinary movements. There may be subluxation of the wrist-joint and marked atrophy of the interossei muscles. The metacarpophalangeal joints may be much relaxed, and there may be great relaxation of the joints of the fingers. The general condition is greatly altered. The patients are emaciated, look sallow and anæmic, and are very weak. With the progress of the disease, deformities are common. The *x*-ray plates show atrophy of the bones, quite different from that seen from disuse. With this the cartilage disappears, and the wrist-joint, for example, may be represented by little more than a structureless mass. The progress is usually downward, and the outlook in this form is extremely grave.

[1] *American Practice of Surgery* (Bryant and Buck), 1907, vol. iii.

3. **Hypertrophic Form** (**Osteo-arthritis**).—In this the changes are more especially in the cartilage and bone, and very varying degrees of involvement are found, both as regards the amount of change in the cartilage and the extent of new bone formation. The other structures do not escape and the synovial membrane may be involved. The form is usually polyarticular and apparently may come on at any age, but the majority of patients are older at the time of onset than those belonging to the peri-articular form. In advanced life the lesions are often more suggestive of degenerative than of inflammatory changes, and yet it has to be remembered that the joints are often seen long after the acute changes are over. There were 60 cases belonging to this form in the series. There are two varieties which require special mention, the so-called Heberden's nodes and the spinal form, the usually termed spondylitis deformans. The term spondylitis includes many varying conditions. As used here the arthritis of the joints of the spine which occurs without any evidence of permanent bony change—already referred to under the discussion of the peri-articular form—has not been termed spondylitis, but arthritis of the spine. In this section the word spondylitis will be used for the cases with evidence of definite bony changes, although really the term includes any inflammatory condition.

Some would doubt the propriety, certainly in many cases, of including spondylitis deformans under arthritis deformans. It is one of the many disputed points. The character of the lesions and the frequent association with the undoubted lesions of arthritis deformans in the peripheral joints seem important evidence to the writer. As already said, changes in the vertebræ frequently go with arthritis elsewhere, and this may be either of the peri-articular or hypertrophic form. Spondylitis occurs with various infections, such as typhoid fever, influenza, gonorrhœa, etc., and the lesions in these apparently do not differ from those found in arthritis deformans.

General Features.—As a rule, the arthritis is polyarticular, the most common exception being the involvement of one hip-joint, the usually termed morbus coxæ senilis. As a rule, the age of the patients is greater than in the peri-articular form. Thus, A. G. Garrod found that among 100 cases, 5 were from thirty to forty years of age, 26 from forty to fifty, 42 from fifty to sixty, 21 from sixty to seventy, and 6 over seventy years. Had the cases of *malum coxæ senile* been included the average would have been higher. Yet the disease may come on earlier than shown by these figures. Thus, in one patient of this series, with the onset at the age of sixteen years, the progress was rapid, and in two years he showed well-marked hypertrophic changes in many joints.

As a rule, the general features are not so severe as in the other form. The arthritis is not so acute, and the temperature and pulse are lower. Thus, among 21 cases of this form, including general hypertrophic and spondylitis cases with sufficiently long records, the temperature was normal in 11, averaged 99° in 2, from 99° to 100° in 4, from 99° to 101° in 2, and from 100° to 102° in 2 cases. In the majority the pulse rate does not go very high. Thus, in 10 of 21 cases it was practically normal; in 6 it averaged from 80 to 90, and in 3 from 90 to 100, only 2 having a pulse rate persistently above 100.

The patient's general condition is much less apt to suffer, and the changes in the joints are much less serious on the whole. The principal effects are

more or less mechanical, and muscular atrophy and contractures occur to a much less degree.

Certain features of the arthritic changes are best described under the various joints.

Heberden's Nodes.—"What are those little hard knobs, about the size of a small pea, which are frequently seen upon the fingers, particularly a little below the top near the joint? They have no connection with the gout, being found in persons who never had it; they continue for life; and being hardly ever attended with pain, or disposed to become sores, are rather unsightly than inconvenient, although they must be some little hindrance to the free use of the fingers." So wrote Heberden under the heading "Digitorum Nodi." Sometimes one is inclined to think this question is still unanswered.

These nodes are small bony outgrowths at the terminal phalangeal joints, sometimes covered by a projection of the synovial membrane. They are more common in advanced years, and are found in many people who have not had any evidence of arthritis elsewhere. They may appear in early life, as in one patient, aged sixteen years, in whom the arthritis began two years before; it was of the peri-articular form in the other joints, but he had definite Heberden's nodes of quite large size. They may be the only manifestation of arthritis which is found; they may occur with a polyarthritis of the peri-articular form or with a spondylitis deformans, being perhaps the only other manifestation. In some cases they are the first manifestation of a general arthritis. In one patient, a woman, aged thirty-two years, they appeared very rapidly on all the fingers.

They only rarely give rise to symptoms, but some patients complain greatly of the pain, which is usually aggravated by much use or by any injury such as caused by knocking the fingers against some hard object. Numbness, a "dead" feeling or tingling, is sometimes complained of, especially by elderly patients. They are unsightly, and frequently cause disturbance on this account. Their distribution is not necessarily regular on the two hands, from one to eight fingers may be involved, and in practically any combination. If one finger is especially used in any occupation, as sewing, the nodes on it are likely to be larger than on the other fingers. Occasionally there may be an active arthritis, and the joints are red, swollen, and painful, as may be seen in one joint following an injury. The onset is sometimes quite acute, and the bony outgrowths appear rapidly after this. The nodes can be readily felt, and stand out markedly in the *x*-ray pictures. Sometimes deflection of the end joint of the finger may be caused by them, although this is not common. They often cause some flexion of the end phalanx, and may interfere considerably with the finer movements of the fingers. Garrod points out that small transparent cystic swellings, which he regards as probably being herniæ of the synovial membranes, are sometimes seen on the postero-lateral aspects of the joints.

The question often arises as to the significance of these nodes. Many patients who have them carry the opinion that they are a manifestation of the effects of "uric acid." In rare cases nodes occur on those joints in association with gout, as Futcher[1] points out. In these cases the nodes rarely occur on many of the fingers, and are accompanied by peri-articular swelling, usually entirely absent when they occur in arthritis deformans. So that, as

[1] In this work, vol. i, p. 830.

a rule, they may be regarded as almost invariably a manifestation of this disease and not of gout. When they occur in patients who have no other arthritic manifestation, it is very difficult to explain their significance.

Thumb.—The carpometacarpal joint is not infrequently attacked. It may be said that involvement of the thumb-joint is more common in arthritis deformans than in any other form of arthritis, acute or chronic. On going carefully over the history it is sometimes found that this was the first joint to be attacked or it may be part of a polyarthritis. There may be a good deal of bony enlargement, with well-marked crepitus, and more complaint of pain in this than in any other joint. The swelling may be quite marked.

Metacarpophalangeal Joints.—These may show marked bony outgrowths, which sometimes are very prominent and project. If with this the joints are much relaxed, great deformity may result.

Hip-joints.—While the involvement of this joint is especially frequent and may be the only manifestation of the disease, as already mentioned in discussing the so-called monarticular forms, yet it may be part of a general arthritis. The more carefully the histories are studied in the cases regarded as monarticular, the more often it will be found that there were previous attacks of acute polyarthritis, which possibly have left but little damage elsewhere, and the more thoroughly the patients are examined, the more often will slight changes be found in other joints. This may be in the form of Heberden's nodes, or perhaps something in a shoulder- or finger-joint. Still, in a great number the principal change is in the hip-joint. As a rule, only one hip-joint is involved.

This form occurs usually in advanced life, although examples in early life are seen. It is much more common in males, and a history of trauma is frequently obtained, although there is often the suspicion that this is secondary to the onset of the process and determined the first marked manifestation. The most marked features are pain and disability. Pain is not constant, but may be very severe. It may be referred to the joint itself or to the groin, or be especially felt in the leg, sometimes along the course of the sciatic nerve and sometimes being referred to the knee or ankle. This sometimes leads to the diagnosis of sciatica, and it has to be remembered that a neuritis may be present secondary to the arthritis, exactly as in the shoulder-joint. Disability may be marked, with definite limitation of motion. The patients often have a characteristic gait, saving the affected leg, perhaps with tilting of the pelvis. Sometimes walking is almost impossible, and going up steps is especially likely to cause pain. The patients get up from a sitting posture slowly, and may have difficulty in crossing the affected leg over the other, perhaps having to use the hands to accomplish this. On movement of the leg there may be severe pain and marked grating. Limitation of motion is especially marked on abduction and inward rotation. Extreme flexion may be impossible. There may be shortening of the leg in advanced stages, due to the bone destruction, but in the early stages it is usually only apparent.

There is commonly some muscular atrophy, which may be marked, and is found principally in the gluteal region, which may show distinct flattening. The knee-jerk of the affected leg is usually increased.

Knee-joint.—This may be involved as part of a more or less general arthritis, but not infrequently this joint suffers more and may be the most severely attacked. There is usually the complaint of pain and stiffness, with difficulty in going up stairs, kneeling or rising from a sitting to a standing position; a

feeling of insecurity with a giving way of the knee is not uncommon. The joint rarely shows much swelling, and in the early stages there is not much restriction of motion. On movements of the joint a loud grating noise may be produced, which Garrod well terms a "scrunch." In the early stages, and some patients do not progress beyond this, it may not be possible to determine that hypertrophic changes are present without the *x*-ray examination. Quite often bony outgrowths from the patella are the first to be recognized by palpation. With progress of the malady, the bony outgrowths become more prominent and may be felt about the femur and tibia. With this there is greater disability and restriction of motion.

The results of the *x*-ray examination suggest that a number of instances of moderate involvement of the knee-joints, seen especially in elderly patients, are of the hypertrophic type. There is but slight arthritis elsewhere, and the process may never advance very far.

Sacro-iliac Joint.—This may be involved, although it may be difficult to determine exactly how much actual change there is in the joint. There is the complaint of pain, which may be referred away from the articulation.

Spondylitis Deformans.—This is sometimes termed "poker-spine, poker-back, or rigidity of the spine," and deserves special attention on account of its frequency and importance. As already noted under the discussion of the polyarticular form, involvement of the joints of the spine may occur without, so far as can be determined, any permanent change remaining. These may be termed spondylitis, but hardly spondylitis deformans, so that here the designation is applied to those cases in which there is evidence of definite structural change.

As has been already mentioned, this condition in the spine may occur as the only manifestation, or may be associated with arthritis of the peripheral joints. Of the 81 cases of spondylitis deformans in this series, in 39 the spine alone was involved, and in 42 this was associated with arthritis elsewhere. While the view is taken here that these changes in the spine are manifestations of arthritis deformans, yet this is by no means the universal opinion, and there has been much controversy regarding both the place of the condition in a general classification and as to whether there are really distinct entities included. Thus, Bechterew has described under the name "Steifigkeit der Wirbelsäule" what he regards as a distinct entity. Strümpell, under the name of "Chronisch ankylosierende Entzündung der Wirbelsäule," and Marie, under the term "Spondylose Rhizomélique," have designated forms with somewhat different manifestations. Many articles have been written on the subject, but the literature is too extensive to be discussed here. A recent article by Rhein[1] gives a summary of much of it. The question as to the identity of the various forms is a difficult one to decide, but when we remember how diverse the manifestations of the disease are in other joints, it does not seem difficult to expect that the same should be true of the spine. The extent of spinal involvement is very variable; in the lower spine the process is frequently most marked on one side, in the cervical region it is much more often on both sides. One patient has the spine alone involved, and then the spine and one hip; another the spine and both shoulders and both hips; one patient has marked signs of pressure over the nerve roots, another has practically none; one patient has kyphosis, another has none;

[1] *Journal of the American Medical Association*, 1908, li, 462.

all these variations are found in such a varying degree that to distinguish various forms from their presence or absence seems a mistake. The writer feels that these descriptions are of various pictures of the spinal manifestations of arthritis deformans.

In the study of the symptoms it is well to have in mind the lesions which are present. These involve an arthritis of the spinal joints, changes in them which are frequently associated with proliferation of bone, atrophy of cartilage with its replacement by bone, and osseous changes in the ligaments. These last are apparently involved very frequently, perhaps the anterior lateral ligament most often of all. The extent of involvement varies greatly, and the process may extend along several vertebræ, making practically a solid column for some distance, or a process of one vertebra may be joined to that of the next one. The transverse processes are not infrequently involved. On account of the anatomical relations, there is frequently some affection of the nerve roots either through extension of the inflammation by contiguity or by pressure. Following this there are symptoms in the distribution of these nerves. Clinically the results of these changes are seen in many ways. Thus, the arthritis causes pain and muscle spasm; if the articulations of the ribs with the vertebræ are involved there is severe pain on breathing, and perhaps almost entire absence of thoracic respiration. The formation of new bone may interfere with the spinal movements, and we have more or less rigidity as a result. If there is rapid destruction of the intervertebral cartilages without their being replaced by bone we have marked bowing of the spine; if there is rapid ankylosis and replacement of the cartilage by bone, the spine is fixed in a straight position, the so-called "poker-spine." The osseous changes in the ligaments give rigidity and limitation of motion. Pressure on or involvement of the nerve roots may give marked sensory disturbances; thus there may be severe abdominal pain or pain in the distribution of the sciatic nerve. When it is also remembered that the process is usually not symmetrical and may involve all or only a part of the spine, the possibilities for great variation in the pictures presented are very evident. This should be kept in mind in the study of the symptoms.

As to the *etiology*, the most reasonable view is that it is due in some way to an infectious process. The changes are exactly like those which have been found in some cases of the so-called typhoid spine, as reported by Silver[1] and the writer.[2] It has long been known that there may be a spondylitis in association with gonorrhœa. Then in some cases the association with some focus of infection may be very definite. Thus, a tonsillitis or an infection of one of the nasal fossæ apparently stands in direct etiological relationship, and with proper treatment of this the spondylitis promptly subsides. The importance of trauma must be noted; sometimes this merely accentuates the symptoms, but in other cases undoubtedly determines their onset.

Occurrence.—This is probably much more frequent than has generally been supposed. In this series there were 81 cases, of which 39 were spondylitis alone and 42 spondylitis with involvement of the peripheral joints. As regards sex, the figures are striking, for it occurs in the great majority of instances in males. As already noted, it makes a great difference in the relative figures for the sexes in arthritis deformans generally as to whether

[1] *American Journal of Orthopedic Surgery*, 1908, v, 194.
[2] *American Journal of the Medical Sciences*, 1906, cxxxii, 878.

or not these cases of spondylitis are included. Of the 81 cases here, 67 were males and 14 females. Of the cases in females, but 3 were spondylitis only, the others were spondylitis with involvement of the peripheral joints. As to *color,* 76 were white and 5 colored. This is a very striking difference, and very difficult to explain. The colored race is just as susceptible to infection, perhaps more so, and trauma must be as common in them as in the whites. It may be said that these figures come from a clinic in which there is a large number of colored patients, and the writer has been on the outlook for the condition in the negro for some years.

Age.—The figures are as follows:

1 to 10 years	0
11 " 20 "	1
21 " 30 "	20
31 " 40 "	29
41 " 50 "	14
51 " 60 "	8
61 " 70 "	7
70 and over	2

There was no special difference in the age in the pure spondylitis cases and in those with other joints involved.

The age at onset in the cases in which this could be determined was:

1 to 10 years	0
11 " 20 "	5
21 " 30 "	24
31 " 40 "	23
41 " 50 "	11
51 " 60 "	7
61 " 70 "	4

In some cases there is difficulty in determining the exact onset, as the history suggests that there have been previous attacks of spondylitis involving a limited part of the spine. Careful inquiry will often bring out this point. It will be seen that the time of onset does not differ greatly from that seen in arthritis deformans generally, although the average is at a slightly earlier age. It is worthy of note that the patients with the onset after the age of sixty years were all examples of spondylitis associated with changes in the peripheral joints, and in all of these the onset was fairly acute. As a rule, the onset was gradual. Trauma, usually described as "strain" while lifting, was associated with the onset in eight cases.

The *complaint* made by the patient is of interest. The largest number complained of pain in the back, but in many there was complaint of pain elsewhere, in the legs, abdomen, or thorax. Several made the complaint of "sciatica." It is well to keep this fact in mind, as there may be no mention whatever of symptoms referred to the back, and attention is easily directed elsewhere. The first symptom varies greatly. In the majority it was pain, referred to the back, hips, or legs, while in others it was referred to the thorax or abdomen. Several complained of stiffness or weakness in the back. Cramps in the legs were the first manifestation in some patients. All of these may be on one or both sides of the body, but in the majority they are more marked on one side than on the other, especially when pain was referred to the legs. The variability in the symptoms is understood if one keeps in mind the anatomical condition.

Throughout the course pain is the most marked *symptom*. This may practically be situated anywhere in the trunk or extremities, but the much greater frequency with which the lower spine is involved explains the corresponding frequency in the symptoms being referred to the legs. The pain may be in the spine, in the course of certain nerves, or in both situations. In some cases the pain may come on in severe attacks, which make the patient cry out. One feature is the onset of pain in the night after the patient has been asleep. This is most frequent when the condition is situated in the lower spine. It is exceedingly common for the general nervous condition of the patient to suffer, for as a result of the wearing pain and disturbed nights the general health is much affected and the patient becomes very neurotic and upset. This is characteristic of spondylitis generally and is especially marked in the form which occurs with typhoid fever. As a result the general nutrition is affected and the patient may lose a great deal of weight. The symptoms may vary a good deal at different times. Some patients are fairly comfortable as long as they are quiet, but any movement stirs up the pain. Others make a special complaint of pain during the night, which may be more or less continuous, or often comes on early in the morning, wakening them from sleep. This is probably due to the muscles being relaxed, and, as it were, off guard, so that sudden movement caused pain.

Examination.—In discussing conditions which are found one must always remember the great variability in the extent of the disease. There are all grades between the patient who has rigidity of the whole spine and the one who has involvement of only two or three vertebræ. The general appearance is sometimes striking. The patient often looks worn, haggard, and sometimes emaciated. The attitude either on standing or walking may be characteristic. If there is general involvement with flexion of the spine the upper part of the body is bent forward, the head projecting, and the eyes fixed on the ground so that the patient has difficulty in looking up. In cases in which fixation has occurred with the spine perfectly straight, the so-called poker back, the patient walks unusually erect. In the cases with limited involvement of the lower spine the patient may limp, and when he stands hold the leg of the affected side with the knee bent. With this there may be distinct tilting of the pelvis. The attitude when the patient is sitting down or getting up is often suggestive. They do these actions slowly, perhaps resting the hands on the thighs, making every effort to avoid bending the spine. If they are asked to stoop and pick up an object from the floor the position is generally very characteristic. They often lower the body by bending the legs and reaching down with the hand, every effort being made to avoid moving the spine. The bony changes and muscle spasm are responsible for the variations.

On examination of the back much or little may be found. The cases of general involvement are so characteristic that they require little description. It may be found that the natural curves of the spine have disappeared, and especially that the lumbar curve is obliterated. In acute cases the condition of the muscles on either side of the spine is sometimes striking. They are markedly contracted and may stand out prominently. This is perhaps most striking when the process is especially on one side, the difference in the state of the muscles being generally very pronounced. The important point is the observation of the movements of the spine. This is done by making the patient stand up, with the feet together, and have him bend forward, bend

back, to either side, and rotate the spine. Some or all of these movements may cause pain, and limitation of motion may be very evident. In the early stages this is rarely equal in all directions; with general fixation, of course, it may be. Thus, there may be marked limitation on bending forward and very little on bending back, or movement may be limited on lateral bending to the right more than to the left. There is very often some limitation of movement on making the attempt to bend backward. Some patients on attempting to bend forward move also somewhat to one side. In bending to the sides it may be found that the freest motion is in different parts of the spine on going to the right and left. Goldthwait[1] has drawn attention to the fact that if the spine be fixed in some special position the motions from that point are freer. Sometimes contraction of the muscles becomes much more evident with the movements. In some instances there may be prominence of the spines of one or two vertebræ, as is sometimes seen at the junction of the cervical and dorsal vertebræ and occasionally in the lumbar region. Occasionally there is distinct tenderness on palpation over particular spines. In cases in which the vertebræ of the neck are involved it may be possible to feel the bony thickening. If this has been especially on one side the head is rigidly fixed in a bent position. There may be involvement of the sacro-iliac joints, and this usually renders the diagnosis difficult from local involvement of the lower spine.

Associated Features.—The frequent complaint of pain in parts other than the back has been noted. This is usually referred to the area of distribution of the nerves, although in some cases there is pain referred to the course of a nerve associated with tenderness on pressure over it. This may especially concern the sciatic nerve, and the ordinary features of sciatica are found. Muscular wasting is quite frequent. This sometimes involves the muscles of the back, but more often those of the leg; thus, there may be marked flattening of one gluteal region, and also wasting of the thigh muscles and those of the leg. As a rule, the reflexes, both the knee-jerks and the tendo Achillis reflex, are markedly increased. This is not invariable, as in a few instances the reflexes were diminished. Ankle clonus was obtained in not a few instances. With the process in the spine largely on one side, muscular wasting and increase in the reflexes may be confined to the leg of the affected side. Disturbances of sensation are common, and there may be marked paræsthesia or anæsthesia. In some cases the former is very marked. The sensory changes may vary from time to time. Irregular jerking movements of the muscles of the legs are sometimes seen.

Features in the thorax are often present if the dorsal vertebræ are involved. Thus, in acute stages with involvement of the articulations between the ribs and vertebræ, pain on breathing may be so severe that the patient makes every effort to spare the thorax and the respiration may be entirely abdominal. It may be noted that the same picture is presented in the cases of general arthritis, with involvement of the joints of the spine. In all these forms as the arthritis subsides, and if there is no fixation, the thoracic movements may be entirely restored. In other cases, however, there may be fixation, which is permanent. If this be associated with bending of the spine the change in the shape of the thorax may be marked, and the costal margin may come to within a short distance of the iliac crests.

[1] *Boston Medical and Surgical Journal*, 1902, clxvi, 299.

X-rays.—The study of the *x*-ray plates is of great importance; changes in the bones and cartilages may be made out, but perhaps the most striking point is the detection of deposits of new bone. These in the majority are extremely irregular, and may be largely on one side, or especially in the anterior ligaments. Thus, irregularity of the process is really the rule, and should be kept in mind in studying these cases. The symptoms suggest, the *x*-ray plates confirm it, as does also the study of museum specimens. The writer went over a large number of these in the London museums and found very few in which the deposit of bone was symmetrical.

Diagnosis.—As in the acute polyarticular form, the knowledge of the condition is an essential to its recognition. The cases of general involvement are so characteristic that a glance is usually enough to give the diagnosis. There is no need to dwell on them, but with the local forms the story is different. We have long been blind to what was before our eyes very frequently. To J. E. Goldthwait,[1] of Boston, much of the credit of drawing attention to these conditions is due.

The symptoms complained of most commonly are stiffness, interference with motion, pain, and muscular weakness. It may be that many of the indefinite pains complained of in the back, especially in the morning on waking, are due to this condition. "Lumbago," while probably rheumatic or gouty in some, is at times due to this. Many of the cases of so-called "sciatica" are caused by arthritis of the spine, and also instances of obscure pains in the legs and about the body. There is no intention of suggesting that every case of pain in the back or of sciatica is due to spondylitis, but it is suggested that in every such case it is most important to examine the back. Some cases otherwise regarded as neurasthenia with complaint of pain in the back will be found to have local arthritis of the spine. Patients complaining of sciatica may have the same condition.

Of the methods of diagnosis first comes the examination of the spine. The patient should be completely stripped, or down to the hips at least. In the majority of cases little is to be made out on inspection. There may be some curvature, or a projecting spine, or more commonly an obliteration of the lumbar curve. Some wasting of the dorsal muscles, or in the gluteal region, or of one or both legs, may be found. In some the attitude is suggestive. They stand with one leg a little flexed and "favor" that side. Next comes the investigation of the mobility of the spine. With the legs straight, the patient is asked to bend forward and touch the floor, bend back and to each side. Any limitation of motion is very readily recognized. This may be equally marked in all directions, or only in one, although usually at least two are combined. He may bend forward but a very short distance, and to one side much less than the other, or lateral movement to one side only may be much restricted. These variations are very readily understood in view of the pathological anatomy. These movements may cause pain, either local or referred. An attempt to bend to the right may cause the same pain in the leg of which the patient complains. The attitude on attempting to pick up an object on the floor is often very characteristic. With this the sensation should be tested; areas of altered conditions are important. The reflexes are usually increased.

The diagnosis may be fairly clear from the examination, but there are two

[1] *Boston Medical and Surgical Journal*, 1899, vol. cxii, and 1902, vol. cxlvi.

important aids—namely, tuberculin and the *x*-ray picture. The use of tuberculin excludes the most common source of difficulty, although tuberculous disease of the spine rarely gives the same disease picture as spondylitis. In some instances there is marked involvement of the hip-joints with the spondylitis, and this may have led to a suspicion of tuberculous hip-joint disease. The radiograph, if it shows anything, is usually characteristic. The deposits of bone usually appear as shadows between the bodies of the vertebræ. In early cases, of course, little may be seen, and in very fat patients it may be difficult to get a clear plate. Should the diagnosis not be certain with any of these methods, one help remains—the therapeutic test. Put a light plaster jacket on the patient, which should extend from the axillæ to the level of the trochanters, and if there is spondylitis there should be marked improvement in the symptoms in a few days. This is especially useful in the cases with sciatica. The possibility of sacro-iliac-joint disease should be kept in mind in obscure cases.

Villous Arthritis.—This is not a distinct entity, but the term is used to describe a condition which may occur from many causes: Trauma, either direct or indirect from flat foot, etc., or from changes in the joint itself, as detachment of a semilunar cartilage; loose bodies in the joint; tuberculosis; syphilis; various forms of infectious arthritis (*e. g.*, gonorrhœal), and not rarely from arthritis deformans. When it occurs as one of the manifestations of arthritis deformans, it has to be regarded as only one part of the general picture.

The degree of proliferation of the fringes varies greatly, from a delicate fringe of membrane to large, irregular masses which may occupy the greater part of the joint cavity. They are usually very vascular, and show both fibrous and fatty tissue.

The knees, shoulder, ankle, and hip are most often involved, the knee being by far the most frequent. In cases in which the condition followed trauma, it is usually monarticular, but when with general disease it may be polyarticular. The symptoms vary with the degree of change. When the fringes are soft they may cause but few symptoms. In the average case there is discomfort in the joint or pain which is rendered worse by use. There is usually considerable general swelling, which suggests marked effusion, and may cause error unless a careful examination is made. The patella may seem to float and fluctuation may be simulated. Tenderness on pressure may be present. When this condition occurs in arthritis deformans one must exclude tuberculosis, gonorrhœal arthritis, a traumatic arthritis, and dislocation of a cartilage. Until one is familiar with the condition, the diagnosis of effusion seems the most likely one; but there is a curious feeling on palpation, which is often very suggestive of a villous arthritis.

Association of Arthritis Deformans with Other Diseases.—The relationship between infective processes of various kinds and these joint conditions has already been noticed. An interesting association is with Raynaud's disease and scleroderma, or both. In this series there were eight patients in whom scleroderma co-existed with the arthritis, and in four of these there was also Raynaud's disease. It is rather striking that in no instance did Raynaud's disease occur alone, but always with scleroderma. In some instances the scleroderma was present first, but in some instances it and the arthritis appeared about the same time and in others the arthritis antedated the scleroderma. Of course, regarding the etiology of these diseases we have little accurate

information, although it is strongly suggested for many reasons that they are trophic disorders. It is quite possible that the infection which determined the arthritis may also influence the nervous system. In these cases there is also evidence of trophic disturbances in the glossy condition of the skin, and sometimes in the state of the nails. In two patients these were much like the changes seen in psoriasis. It was rather striking that the examples of these combinations occurred in women, and nearly all of them were patients of a marked neurotic character, it being necessary to keep in mind, however, that the state of the nervous system is largely secondary to the disturbance of the arthritis. As a rule, the outlook does not seem to be good in this group. The scleroderma seems to have a marked tendency to progress.

Spiller[1] has drawn attention to points of resemblance between paralysis agitans and arthritis deformans in the report of a curious case in which both diseases were probably present.

In the Cambridge report attention is drawn to a group of cases which show lesions suggesting both gout and arthritis deformans. These are puzzling and their exact nature is not decided.

Diagnosis.—It may be thought that the question of diagnosis would be a difficult one in a disease about which there is so much confusion and which may really include various diseases. Yet actually when the problem is faced the difficulties are not so great. They may be regarded as generally belonging to one of two classes: (*a*) in which the condition is acute and the deforming changes are not greatly in evidence, and (*b*) in which chronic changes have appeared. In the first group it may be difficult to form a definite opinion for some time; in the second we know that the number of diseases causing deformity of the joints is not so large that differentiation is often difficult.

Certain points may be mentioned. That a thorough examination is important seems unnecessary to say, and yet the diagnosis of an arthritis in the larger joints may be cleared up by finding slight changes from a previous attack, perhaps in one finger-joint. An arthritis which recurs and which has left permanent damage in a previous attack is usually arthritis deformans, gout being excluded. Then it is important to learn that this disease may begin suddenly as an acute polyarthritis, which too often is regarded as excluding it. The character of the fever curve, the rapid pulse, the special joint changes, are all aids. In the more chronic forms the diagnosis is rarely in doubt, but unfortunately at this time the benefit of early diagnosis is gone.

Certain characteristics of the arthritis are important. Perhaps the most marked is that when a joint is attacked the condition rarely clears up except very slowly, and there is always a tendency to some change. If it be kept in mind that acute rheumatic fever does not leave any permanent change in a joint, one frequent source of error will be avoided. (It may be said that this view is contrary to that held by some observers, but the writer can only say that for a good many years he has been looking for a patient with acute rheumatic fever in whom permanent changes in the joints remained after an attack, and has yet to find one.) Location in certain joints is often suggestive. Thus, to have involvement of the joints of the cervical vertebræ, the temporomaxillary-joint or the thumb-joint, in association with arthritis elsewhere, is often suggestive of arthritis deformans. Involvement of one or

[1] *University of Pennsylvania Medical Bulletin*, 1904, xvii.

two finger-joints is likewise suspicious. Permanent changes in the joints may be found early; for example, the capsule of the knee-joint may show definite thickening, or there may be distinct thickening about a finger-joint soon after the onset.

The greatest aid is given by the *x*-ray examination, which should always be made in a doubtful case. The plate not only gives aid in determining the diagnosis, but also in regard to the particular form of arthritis deformans which is present.

In distinguishing this disease from others, it is convenient to consider, first, the more acute forms, remembering that what is to be a chronic arthritis may have acute features at onset, and, secondly, the more chronic forms. Among the acute diseases which cause difficulty are the following:

1. **Rheumatic Fever.**—It may be quite impossible at first to distinguish this. The usual mistake is to regard an acute form of arthritis deformans as rheumatic fever, rather than the reverse. Knowledge of how often arthritis deformans begins suddenly as a polyarthritis with acute features is an aid. There is rarely any shifting from joint to joint in arthritis deformans, and a joint once attacked stays affected. The character of the arthritis is different, as a rule. The joints are usually not so tender to the touch as in rheumatic fever, there is rarely the same degree of redness, and it can sometimes be made out that the swelling is more in the surrounding tissue than in the joint itself. Certain joints, especially those of the neck, the temporomaxillary joint, and those of the thumb, are rarely attacked in rheumatic fever. The involvement of the finger-joints is often very characteristic. The temperature in arthritis deformans is usually not as high as in rheumatic fever, the degree of arthritis being considered, while the pulse rate may be much higher relatively than the fever. Persistence of a high pulse rate after the subsiding of the acute joint features is suggestive of arthritis deformans. The enlargement of the associated lymph glands is usually greater than in rheumatic fever. Rapid muscular atrophy, especially of the interossei muscles, is suggestive, as it is more likely to occur with arthritis deformans. The lack of response to treatment with the salicylates may excite suspicion. In a doubtful case the first clue is usually given by the persistence of changes in the joints. This should always suggest a reconsideration if the diagnosis of rheumatic fever has been made. In all cases of acute polyarthritis in which there is some question as to the nature, the diagnosis of rheumatic fever should be the last to be made and not the first, as is usually the case.

2. **Gonorrhœal Arthritis.**—This undoubtedly is the most difficult disease to distinguish. Keeping in mind the history and making a thorough search for gonococci are the great safeguards. The clinical features are much the same as in arthritis deformans, but there is often more synovitis associated. There is rarely the involvement of the joints of the hands as in arthritis deformans. The brunt of the attack in gonorrhœal arthritis often falls especially on one joint, although several joints are attacked. Determination of the opsonic index to gonococci may be of help.

3. **Gout.**—This may appear as an acute polyarthritis and cause difficulty for a few days, but usually not for long, unless it be one of the cases of gout which has a prolonged course of acute features. The absence of marked changes in the joints and the results of treatment are suggestive. The finding of tophi and sometimes a study of the uric acid excretion aids its recognition. In some cases of chronic gout without any special distinguishing

features the diagnosis may be difficult. The relative frequency of the diseases should be kept in mind; arthritis deformans is much the more frequent.

4. **Some of the Forms of the So-called "Infectious" Arthritis.**—This group may pass over into arthritis deformans, and it is difficult to know where to draw the line. The frequent occurrence of arthritis with or after many acute infections has to be always remembered. It is sometimes especially important for prognosis to distinguish them, but this may be difficult until time gives the answer. The knowledge of a source of infection, the results of treating this, the progress of the arthritis, and time are our greatest aids.

Certain forms of arthritis deformans require special mention.

(*a*) *The So-called Still's Disease.*—This is not likely to give much difficulty, as the picture it presents is usually characteristic in the association of a multiple arthritis, especially with peri-articular changes, marked general glandular enlargement, and an enlarged spleen. In some cases a general tuberculous arthritis may give difficulty, but the *x*-ray plates and the use of tuberculin should settle the question.

(*b*) *The "Monarticular" Form.*—This term is only used for clinical convenience. On careful examination slight changes in other joints can usually be found. The greatest difficulty arises in the shoulder-joint where two conditions especially cause error. One is neuritis, arthritis often being regarded as this, and the other is subdeltoid bursitis, which is usually regarded as arthritis. The diagnosis of neuritis may be correct so far as it goes, but it is secondary to arthritis. Careful examination will usually show signs of arthritis, if this be kept in mind, as a cause of neuritis in the arm. The features of subdeltoid bursitis should be looked for, and it will usually be found that the joint itself is free. In subdeltoid bursitis there is pain when any attempt is made to abduct the arm, or it may be elicited by pressure over the bursa. Occasionally the pain is referred along the bicipital groove or down the arm. There is marked restriction of motion, especially abduction, and internal rotation is usually markedly limited. Sometimes the swollen bursa may be felt. In long-continued cases there may be atrophy of the muscles of the shoulder girdle. Sometimes, however, the exact diagnosis may be difficult, and then the *x*-ray plate is useful as determining the presence or absence of joint changes.

In the hip-joint there is usually less difficulty, although sometimes the condition is regarded as tuberculous. The tuberculin test is useful. If there be communicated inflammation to the sciatic nerve the diagnosis of neuritis may be made. Knowledge of the possibility of this error is a great aid in avoiding it. Disease of the sacro-iliac-joint may cause error. Search for the signs of disease there will usually prevent this.

(*c*) *Arthritis of the Spine.*—This occurs at times apart from any evidence of hypertrophic change, although the majority of these cases belong there. As a rule, the most common symptom is pain, which may be in the spine itself—as is seen especially in the cervical region—or referred to the distribution area of certain nerves. Thus, occasionally there may be pain in the track of the nerves of the brachial plexus, or more commonly it is in the sciatic nerve. Careful examination of the spine usually gives the diagnosis. Pain on any movement and restriction of motion are most common. The limitation of movement may be only in one direction, even when the subsequent course shows that there is no new formation of bone.

(*d*) *Atrophic Form.*—It is often possible to recognize this form before making the *x*-ray examination, which makes the diagnosis certain. The joints show marked degeneration, partial dislocation occurs early, muscular atrophy is often rapid in its appearance and progress, and there may be pronounced grating in the affected joints. In interpreting the *x*-ray plates, it must be remembered that there may be a certain amount of bony atrophy secondary to any continued arthritis. Such should not be mistaken for this form.

(*e*) *Hypertrophic Form.*—While the examination of the joints may serve to distinguish this at a glance, as in the Heberden's nodes, yet in the larger joints the chief dependence must be placed on the *x*-ray plates. In a joint—such as the knee—with marked muscular atrophy above and below, there is often the suggestion that there is enlargement of the bones; the *x*-ray plate frequently shows that this is not the case. Of special forms, the Heberden's nodes rarely give any difficulty, especially if several joints are involved. Injury, however, may have results which closely resemble them, but this rarely affects more than one or two joints.

(*f*) *Spondylitis* demands special attention. In pronounced cases, with the whole or greater part of the spine involved, there is no difficulty. It is in the early stages or in the cases with local involvement that greater difficulty arises. The patient's attitude may be characteristic. He may stand with one knee bent or evidently favor one side. His general movements may be suggestive; thus, he may stand up or sit down with the spine held stiffly or stoop down without bending the spine. In some cases he uses his hands to "climb up his legs" when changing from a stooping to a standing position. Examination of the back may show little or the lumbar curve may be less marked than normal. In rare cases some of the spinous processes may be more prominent. The muscles on one or both sides of the spine may stand out, and on palpation be felt rigidly contracted. Investigation of the movements is most important. With the patient standing with the feet close together, he is asked to bend forward, backward, and laterally, and then to twist the spine. Any interference with movement is then readily made out. The movements or attempts to make them may cause referred pain, which often aids in the exact diagnosis. The *x*-ray plate is usually confirmative if the process has advanced to the formation of new bone. If there be any question as to the diagnosis from tuberculosis of the spine, tuberculin may be given. The cases of spondylitis with involvement also of the shoulder- or hip-joints rarely give any difficulty. In some cases disease of the sacro-iliac-joint may cause confusion, but the signs of this are fairly characteristic. The therapeutic test is at times of value. A properly applied plaster jacket may give relief to the symptoms.

There are certain ailments which may cause confusion, these usually being regarded as arthritis deformans. Sprains, pain due to muscular strain, pain due to certain occupations, relaxation of ligaments, flat foot, neuritis, lumbago, and such like, can generally be excluded or recognized by careful examination.

The *x*-ray examination is always of the greatest help not only in deciding as to whether or not arthritis is present and its nature, but also in giving information as to the degree of change of the joint. To estimate this last should always be our aim. To know the form we are dealing with is important both for prognosis and treatment. To know how much change there has been in the joint is essential for proper and intelligent handling, and should be as much a part of the diagnosis as the determination of the disease itself.

Prognosis.—In forecasting the outlook in a disease with so many varying features, it is evident that much has to be left to the judgment of the physician and the conditions in a particular patient. There is no general rule which we can apply. The type of disease makes a great difference as well as the general character of the patient. Speaking generally, the writer is inclined to be more hopeful about the outlook than the majority of those who have discussed the disease. There are certain exceptions which will be noted. Let it be said that there is no intention of minimizing in any way the gravity of chronic arthritis. To fight a winning battle with one of the most intractable of chronic maladies, not as regards life but for the comfort and usefulness of the patient, it is necessary to know the power of the enemy and to have a wholesome respect for the dangers. Perhaps nothing has given more personal encouragement than the results which have been obtained in dispensary practice. To get hold of patients early in the course, teach them what to do, have them work enthusiastically despite discouragements, and finally get through without much damage is cheering. To see a patient grow steadily worse despite all treatment dampens our enthusiasm. Yet it is important both for the physician and patient that the most cheerful view be taken, for both will work harder. The character of the patient must always be taken into account. Some will work hard, others expect everything to be done for them. The condition of the nervous system is often important. High-strung, nervous patients often do badly, and any such condition is usually aggravated by the arthritis.

The various forms deserve special mention. The proper recognition of the form which is being dealt with is most important in the prognosis as well as the degree of damage done to the joint. For this the *x*-ray examination is most useful.

1. **Peri-articular Form.**—Here there are many factors to be considered. (*a*) *Early Diagnosis:* This is most essential, in order that proper treatment may be begun early and that no treatment will be carried out which will do harm. (*b*) *Recognition of the Cause:* If the local focus of infection can be found and properly treated before great arthritic damage is done, the outlook is much more encouraging than when the contrary is the case. (*c*) *Age:* Generally the older the patient the better the outlook, although this is not always true. In older patients there is sometimes a tendency to slowly progressive degenerative changes. (*d*) *Station in Life:* While in some cases the possession of wealth and the ability to have expensive treatment, such as massage, is of benefit, yet often the poor, who have the stimulus of necessity, seem to do better. Too often the rich are able to lie back and be waited on, to their ultimate sorrow, while the exertion demanded of the poor may be their greatest aid. (*e*) *Character of the Patient:* This means a great deal. Those who fight and "never say die," always working, as a rule, do well; but those who lie back and demand that the physician do everything, who are willing to take medicine but not to exercise, generally do badly. (*f*) *Character of the Attack:* The severity of the initial attack is no guide to the ultimate result. As a rule, in the patients with acute attacks the outlook is much better than in those with a slow progressive process which advances steadily from joint to joint. The attacks which begin in women about the menopause always demand a very guarded prognosis. The outlook in them is likely to be bad. The acute progressive cases can usually be recognized, and in them a very guarded prognosis should always be given. (*g*) *General*

Nutrition: This is important, and in patients whose nutrition is much affected and who do not respond to good hygiene, diet, etc., the outlook is always more serious than in those who can be well nourished.

There are some local features in the joints which are of aid. (*a*) *Pain:* The degree of this is no indication of the severity of the arthritis, and yet its influence on the general health of the patient cannot be disregarded. Its presence may hinder use of the joints and favor ankylosis. It may be practically impossible for the patients who have severe pains in the feet to walk and obtain sufficient exercise. (*b*) *Changes in the Joints:* These are important, and for this the use of the *x*-rays has been of great aid. With joints in which the changes are entirely peri-articular and the cartilage and bone show no change, the outlook is better than when signs of erosion and thinning of the cartilage are evident. Here, however, caution is needful, for the cartilage which shows no change to-day may do so in six months or a year. (*c*) *Joints Involved:* This is sometimes a help. The elbows if attacked often show marked permanent changes, the wrists and shoulders much less. Marked changes about the knuckles and finger-joints are often suggestive of much future deformity. The hip-joints have a tendency to permanent fixation. The knees easily become flexed, and arthritis of the joints of the feet may be very crippling without much actual change. The neck and jaws usually do well.

In the "monarticular form" the outlook, as a rule, is good for fair, ultimate recovery, but generally one cannot prevent the rather long duration. Some of the patients with marked atrophy of the muscles may be two years before reaching a fair degree of recovery. In the so-called Still's disease, the majority of writers regard the condition as practically hopeless, death usually occurring after some time. The experience of this clinic, however, has been much more encouraging, although we have only had a few cases, yet several of them have done extremely well and have shown almost complete recovery.

In all the cases of this group certain features are of importance in estimating the outlook. If there be marked muscular atrophy which has come on rapidly, the outlook, as a rule, is more serious. If there be marked early tendency to contracture, it is always well to be cautious. Then the patients with marked general nervous disturbance, as a rule, do not do very well. With this seems to come an intolerance of pain, so that it is impossible to carry out the usual measures to prevent ankylosis and contracture. Naturally in a disease which is so often accompanied by general disturbance of nutrition the condition of digestion is important. In patients who are unable to take enough nourishment or whose digestion is easily upset, one should always give a guarded prognosis.

2. **Atrophic Form.**—In this it may be said in a general way the outlook is always serious. We do not seem to have any means of hindering the progress of the disease, which, as a rule, progresses to more and more disintegration and destruction of the joints. No matter how slight the early changes may seem to be, or how good the patient's general condition, the prognosis should always be guarded, because, as a rule, there is the tendency to subsequent advance which apparently we cannot prevent in the majority of cases. The general condition is often the best guide as to the outlook.

3. **Hypertrophic Form.**—In this the outlook depends on many different features and no general statement can be applied to them. (*a*) *Heberden's*

Nodes: As regards any possibility of absorption of these there is only one answer to give: Once present, they are permanent. However, beyond the appearance and slight discomfort, they rarely give any severe trouble. If they are painful, one can usually assure the patient that this will not last for a great time. Much depends on the patient's avoidance of injury, and this influences the outlook to a considerable extent. (*b*) *Conditions in the Larger Joints of Elderly Patients:* Although the general tendency is toward slow progression, yet the outlook is in many instances better than one might have expected. It is never safe to be too positive about the outlook in either direction, and it is not unusual to find them doing much better or much worse than one expected. However, as a rule, the possibility of complete recovery is almost out of the question. (*c*) *Smaller Joints:* Although the condition may not advance very materially and a fairly good prognosis is often justified, it must always be remembered that bony outgrowths having once formed cannot be removed unless by surgical measures, which are sometimes indicated. The hope is that further progress will be prevented, and the patient's condition not become worse than it is. (*d*) *Spondylitis:* In this the outlook depends very largely on how much of the spine is involved. If the patients are seen in the acute stages a good prognosis can usually be given as regards the freedom from pain, but the amount of disability cannot be estimated. If the process is at all general there may be rigidity of the whole spine, with more or less deformity, although it is always encouraging that the extent of the fixation rarely corresponds with the extent of acute arthritis. In the cases of local involvement, as, for example, in the lower spine, the outlook is generally good if treatment has been begun early. The process is usually confined to a few vertebræ, and the patient recovers with very little disability. The possibility of subsequent attacks involving more vertebræ can never be excluded.

In all forms the general condition of the patient is the important factor, and the possibilities of good surroundings and proper nutrition must always be considered. As has already been said, the outlook depends a great deal on the patience and perseverance of the patient and physician. The possible effect of some intercurrent acute infection is difficult to forecast. While, as a rule, any such tends to aggravate the arthritis, as, for example, an attack of influenza, yet in some patients the state of the joints is much better after an acute attack of another disease.

In all acute cases two questions arise—the outlook in the immediate attack, and the ultimate result in the joints. As noted, the acute attacks are usually over sooner and often leave but little damage. The general features, such as fever, and the arthritic conditions are both important, but it is never wise to prophesy too much. In the slowly advancing form the prognosis should always be very guarded. As to the ultimate result in the joints, the *x*-ray examination is always of great value. If this shows peri-articular change only, the outlook is usually good; but if early erosion and destruction of the cartilage is found, one must be very cautious.

In cases with marked changes, the question as to possible restoration of function is also greatly aided by the radiograph. With damaged articular surfaces, displacement, or marked atrophy the outlook is never good. If the joint surfaces are not damaged, even with a good deal of contraction, it may be possible to get back function in a wonderful way. The possibility of aid from surgical intervention should always be taken into account.

Treatment.—It is evident that in a disease which has so many different manifestations and methods of progress no scheme of treatment can be laid down which will apply to all patients. Again, it is a disease at times characterized by acute attacks which may end as such or pass over into a chronic stage, or it may be chronic from the onset. Then, too, in its treatment both the general condition of the patient and the state of the joints have to be considered. It is well to emphasize the fact that treatment to be of avail must extend over a long period of time. Dogged perseverance must be shown both by the physician and by the patient. Too often both lose patience and part company, the patient to see if some other practitioner (too often some quack) cannot help him more, the physician perhaps with a feeling of relief that this particular knotty problem has gone to someone else. Perhaps more than of any other disease is it true of this one that the patients rarely go through a very long siege of the malady without seeing many physicians.

The subject has its dark and its bright side. When one sees a patient in whom the disease progressively advances, crippling one joint after another, more or less steadily advancing in many joints despite all treatment, the feeling of hopelessness and helplessness cannot be escaped. At the opposite extreme, when a dispensary patient steadily improves, even under adverse circumstances, one feels that there is some hope for the majority. It may be said that this is no disease to be treated by medicines alone. The physician must be prepared to work hard and keep his patient working hard—often a much more difficult task. The whole mode of life must be supervised and constant attention paid to every detail. There must be much the same attention given to every point as in the case of a patient who has pulmonary tuberculosis.

At the risk of tiresome repetition, the need of early diagnosis must be emphasized again. It seems absurd to insist on this so often did not the history of many patients prove the contrary. The great hope for many of them lies in early recognition and proper handling. Too often the error is made of regarding the disease as "rheumatism," after which almost everything done for the patient is more likely to harm than to help him. To keep the patient indoors, to cut off protein food, to give prolonged hot baths, to administer large doses of salicylates, are all injurious as a rule. After the disease has run its course, the effort to restore function to greatly damaged joints must often be fruitless. Early recognition and then persistent treatment are all important.

The treatment of a given patient generally has to be considered from two points: (*a*) that of the general condition, and (*b*) that of the joints. On the whole, the former is the more important; the whole is greater than the part, and if the individual is doing badly, his joints are not likely to do well. Every disturbance of the general health should be regarded seriously, and these patients should take unusual precautions with any slight infection, gastrointestinal trouble, etc. It seems as if their equilibrium rested on a narrow support and was readily upset, usually with harmful results.

Source of Infection.—In line with the view that the disease is dependent on some infection, every effort should be made to discover a primary focus, if such exist. This demands very thorough investigation—there is no use in half-way measures. If definite change has occurred in the joints, the removal of the original source of infection will not result in complete recovery, but it will probably stop any advance of the process. The condition of the

mouth must be first looked to, carious teeth should receive attention, and pyorrhœa alveolaris should be treated. The tonsils should always be carefully examined. If they show obvious infection, there is no doubt as to the advisability of removal. If there be no direct evidence of involvement, the decision is more difficult. Frequently a tonsil which shows no surface evidence of disease, after removal shows some deep pockets which contain streptococci. If there is any doubt as to the condition of the tonsils, it is better to give the patient the benefit and advise removal. This should be thorough; nothing short of complete removal by dissection is sufficient. To remove only the superficial part can rarely be of essential benefit. Careful examination should always be made for any focus of infection in the nasal sinuses and alveolar processes. Otitis media should be treated if present.

The respiratory tract does not offer many examples of the source of infection being there, yet a persistent bronchitis may have an influence and should be treated. In the same way any gastro-intestinal disturbance should receive attention. The effort should be made to correct any digestive disturbance. How much intestinal disturbances may be causal factors we do not know; but, at any rate, for the sake of the general nutrition, if for nothing else, we should try to prevent them. Dysentery especially should be thoroughly treated. Some patients in whom there is no definite intestinal disturbance are helped by free purgation, and others by daily washing out of the colon.

Next to the mouth and pharynx, perhaps the genito-urinary organs are the most important causes of infection. In males, it is especially necessary to investigate carefully the prostate gland and seminal vesicles. The contents should be massaged out and thoroughly examined. In women, the possibility of any infection of the urinary tract and the condition of the pelvic organs should be determined. Any source of infection, such as an open sinus, should receive attention.

If local trouble is found anywhere, the measures which are demanded for its treatment should be carried out. They need not be discussed in detail. The question sometimes arises as to whether any severe local treatment—such as removal of the tonsils—should be carried out while the patient is having acute arthritic symptoms and perhaps fever. If we are correct in attributing the condition to the local focus, there is every reason why this should be treated at once. An analogous case is seen in gonorrhœal arthritis, in which it is equally important to treat the urethritis as the condition in the joint.

General Considerations.—This is a debilitating disease, and the importance of this should be kept always in mind. No measure should be adopted which can affect the general condition unfavorably or in any way reduce the patient's resistance. The better the patient's general condition, the better for his joints.

Hygiene.—The patients should have all the fresh air and sunlight possible. If able to walk they should be outdoors whenever possible. If unable to do this, perhaps owing to general involvement or acute remissions, they should be kept outdoors as much as can be managed, exactly as the patient with pulmonary tuberculosis. They are often benefited by sleeping outdoors. In cold weather it is necessary to see that they are properly clothed, and the extremities especially should be kept warm. It is important to protect them against sudden changes of temperature. In patients with marked involvement of the hands or feet, comfort is often given by having them wear bed

socks or woollen gloves at night. Some patients are helped by periods of rest each day.

Diet.—In general, it may be said that there is only one regimen for patients with this disease, and that is *full diet.* Of course, individual peculiarities and special conditions have to be considered—that is common-sense. The diet should be chosen which agrees best with the patient. In addition to the regular meals, it is well for a time to give extra nourishment between meals and at bedtime. This may be in the form of milk, eggs, cocoa, etc. One very common error is to diminish or cut off as far as possible all the proteins from the diet, it being often suggested that the disease has something to do with uric acid. This almost always results in harm, and sometimes very serious harm. The writer would lay special stress on this, and emphasize the injury done by restricting the diet for no other reason than this. It is probably under the mark to say that one-half of the patients who have the disease to-day are on a restricted protein diet, and thereby being harmed. If anything is to be cut off from the diet it is usually better to reduce the carbohydrates, as many of the patients are subject to some digestive disturbances which are aggravated by too much of this form of food. A full protein diet is usually indicated, and, as a rule, the fats are well taken. Some are helped by the use of the fermented milk preparations. If the patients are accustomed to alcohol there is no reason why moderate amounts should not be given. As a rule, large amounts of water should be taken to favor elimination. There is no special virtue in any particular water, except that some patients can be induced to drink more when some special name is attached. It is best given rather before than with or immediately after meals.

Bathing.—Apart from some of the measures of local hydrotherapy, such as douches, compresses, etc., bathing is not of value, as a rule, in the *acute* stages; in fact, it is often positively harmful. Prolonged hot baths are often debilitating and should not be given. A sojourn at various springs is usually of more value from the change than from any special virtue in the baths. While this applies especially to this country, it must be recognized that in England such places as Bath have a reputation in the treatment of this disease.

Massage.—The majority of patients are helped by general massage; that of the joints will be discussed later. It aids the general condition and helps to lessen the amount of muscle atrophy. Care should always be taken to see that it is not given too vigorously, a mistake often made by those who give massage. Many of these patients are exhausted after any but the lightest rubbing, so that this, certainly at first, should be as light as possible, and increase in the vigor with which the massage is given must be very gradual. Two or three times a week is usually enough for general massage. The use of some form of vibratory movements is useful in some cases.

Electricity.—This is sometimes used, and some favorable reports have been given, especially from the use of electric light baths, which probably owe their effect to their influence on nutrition.

Climate.—There is no doubt of the benefit of a change of climate, especially from the North to the South in winter. Whether this is due to anything more than the possibility of being more outdoors and leading a life more in the open air is difficult to say. The more equal climate undoubtedly has an influence. Certain patients are more apt to have recurrences in colder weather, and improve immediately with a change to a warmer climate. As a rule, a dry, equable climate suits the patients best.

Occupation.—The English writers especially lay great stress on occupations, such as washing, which involve much wetting, as tending to aggravate the disease. This is not very evident in the study of the cases in this series. It sometimes has a marked influence, but unfortunately the patients in whom this is seen are often the ones who do not have it in their power to change. Some patients who work in damp surroundings are helped by a change of occupation. Attention should also be paid to the house, and if this is damp another one should be chosen.

Medicinal.—That we possess any drug which essentially influences the disease there is no evidence. Naturally, in a debilitating disease, it is important to keep the blood in as good condition as possible, and for this iron and arsenic are perhaps best, the iron being given as Blaud's pills and the arsenic as arsenous acid combined with Blaud's pill or in the form of Fowler's solution. Many patients do very well on the syrup of the iodide of iron, which may be given in full doses over a considerable time. Some few patients are benefited by potassium iodide given persistently. That any of the salicylate preparations are of value is doubtful. They may be used for pain, but their long-continued use in the hope of influencing the disease is not advisable, as they often do harm. Guaiacol carbonate in doses of gr. v (gm. 0.3) is strongly advised by many of the English writers. Some have obtained good results from iodine in the form of the tincture in doses of ♏j to ij, especially in acute attacks. There is no evidence that lithia has any influence on the disease.

Pain is one symptom which often requires general treatment. Few patients escape this entirely, but in many the various local measures to the joints are sufficient to give relief. Some patients have such severe general pains that drugs must be given. The salicylates, aspirin in doses of gr. vij (gm. 0.5) or more, guaiacol carbonate, gr. v (gm. 0.3), antipyrine, gr. iij (gm. 0.2), sometimes combined with codeia, gr. $\frac{1}{4}$ (gm. 0.016), may be tried. Morphine should not be given, as there is great danger of its becoming a habit.

Marshall has drawn attention to the effect of ether, administered as a general anæsthetic, on the arthritis especially when very acute. The ether is given in the usual way for about fifteen minutes. The pain is sometimes markedly diminished and the condition of the joints improves. The period of improvement varies from a few days to two weeks. This is worthy of a trial in severe attacks.

Treatment of the Joints.—Here only general indications can be given, and every patient must be carefully studied. It is always important to be sure that we are not doing any harm. The various forms demand different handling, and a degree of exercise which is of great help to a patient with marked peri-articular changes may be harmful to one with hypertrophic changes predominating. As a guide to treatment, the study of the *x*-ray plates is of great aid. Thus, if there is marked destruction of the cartilage or hypertrophic bony changes it is evident in a general way that rest is important and exercise harmful, which if the changes are peri-articular we are usually safe in advising use.

Peri-articular Form.—In general terms it may be said that exercise and use of the joints are beneficial. This is probably for several reasons, the nutrition of the structures is better, the risk of ankylosis and muscular atrophy is diminished, and the chance of contractures is lessened. This is well seen in the temporomaxillary joint, which is relatively often affected, but which

rarely shows ankylosis. Talking and chewing are two exercises which keep it from fixation. One caution is important—use should not be begun too soon. Rest should be the rule so long as the condition is acute. Yet even here there are exceptions, and sometimes it is well to begin gentle massage and movements before the acute features have entirely disappeared. Care should be exercised in the use of fixation as a therapeutic measure. Atrophy, adhesions, and contractures may appear with great rapidity.

Passive Movements.—These may often be begun early. They should be carried out gently at first and increased as the condition warrants. The production of pain is not necessarily a contra-indication, and especially when there is a tendency to contracture. Some patients have pain at first on the gentlest movement, but this usually lessens with use. The early use of passive motion is of great value in preventing adhesions.

Massage.—This is often our most helpful measure. It must be begun gradually and increased slowly. It is important to oversee this point, as many of those giving massage are likely to be too energetic. Gentle kneading and circular movements about the joint are the most useful. For the muscles above or below the joint more vigorous measures may be used. If there is severe pain it is often advisable to have the rubbing done after the use of measures, such as hyperæmia, which ease the pain. The patients can often be taught to do a certain amount themselves. They can work on the hands and wrists very well after being shown how to perform a kneading motion with the thumb on one surface of the hand and the fingers on the other. This is more useful than mere surface rubbing. In this way they can work over all the joints of the hands and wrists. One advantage of this is that they are doing good to both hands at the same time. They can sometimes work at the elbows, knees, or feet in the same way.

Exercises.—These are useful. The patient should be started at very simple ones in the beginning. Thus, with the hand they may begin by making a fist and alternately spreading the fingers and bringing them together. A rubber ball with a small hole in it which they can squeeze in the hand is of help to many. Various movements at the wrists, elbows, and shoulders may be done. Lifting the shoulders, rotating the arm, raising it up, etc., may all be tried. In the same way the knees, ankles, and toes may be exercised. It is sometimes an advantage to have them keep a record from day to day of the exercises and the number of times each was done. Certain forms of mechanical apparatus may be used in the giving of exercises. In all of these it is important to go slowly at first, and always stop short of fatigue, as this is usually harmful. The patient's strength should be estimated, and the number of exercises and the number of times each is to be done carefully ordered. Increase should be very gradual. One great advantage of the exercises done by the patient is that it gives them a feeling of doing something for themselves and of making a personal fight. This should be taken advantage of in a disease in which there is so much excuse for the patient to lie back and "let things go."

Counterirritation.—This is often of great help, both for the pain and to aid the local nutrition. The Pacquelin cautery lightly applied, blisters, mustard, or iodine may all be used. Repeated small blisters are usually better than one large one. Baking may be considered here. This may aid the blood supply, but it is chiefly of help in easing pain. Care should be taken not to give the treatment for too long a time; twenty to thirty minutes is usually enough.

The temperature in the oven may be raised to 350° F., but there is usually no advantage in reaching the highest temperature which the patient can stand. It is well not to cover the joint with too much material. Care should be taken not to allow the patient to become chilled afterward, especially if there has been sweating. The frequency with which baking is done depends on the severity of the condition and how the patient reacts. Once a day is generally sufficient for severe cases; in others two or three times a week is sufficient.

Hyperæmia.—This is sometimes of great aid both in influencing the process in the joint and relieving pain. No rule can be made as to whether active or passive hyperæmia will afford the greatest relief in a given case. In using the Bier methods (the bandage, etc.) the bandage should be put on above the joint with sufficient pressure to interfere with the venous return, but not with the arterial flow. The necessary pressure can usually soon be determined for each patient. At first the bandage is left on for an hour at a time, but this can be increased rapidly until it is on for eight, twelve, or even twenty hours. Some patients prefer to have it put on at bedtime and left on during the night. It is not uncommon to have some transient œdema as a result, but this need not cause any uneasiness. Another method is to empty the limb of blood as much as possible by elevation and stroking toward the body, after which a bandage is applied, with pressure sufficient to stop the arterial flow. This may be left on from thirty seconds to one minute, and is then removed. This should not be done more frequently than once a day. The use of the suction methods for producing hyperæmia are sometimes of value, but, as a rule, not to the same extent as the others.

Prevention of Deformity.—This is most important, and prevention is much easier to carry out than cure after deformity has occurred. Use of the joints and local exercise and massage are perhaps the greatest aids. Every effort should be made to prevent contractures, which are usually most apt to occur in the elbow and knee. By perseverence much can be done, but in some patients it seems almost impossible to prevent contractures, owing to the pain caused by any manipulation or the marked constant contraction of the muscles. In such it may be well to put the joint in a splint for part of the day or use light extension for some hours each day. The danger of putting joints up in plaster casts for several weeks should be recognized, and this is rarely advisable. In some patients the injection of oil into the cavity of the knee-joint may be of value. Persistent exercises and passive motion are helpful for the shoulders.

For the hands a certain amount can be done by the use of light splints, well padded, which may be worn at night. The tendency to flexion at the first interphalangeal joint and to hyperextension at the proximal joint can be considerably lessened by this. In some patients it seems that the tendency to ulnar deflection can be diminished by the use of a light splint, although one must not hope for too much from this.

Treatment of Deformity When Present.—At first sight the hope of doing much for already established deformity often seems slight, and yet it is surprising what can be done by persistent effort. The employment of various forms of machines for giving the exercises is of great service in these cases. The patients should be encouraged to work themselves in every possible way. Sometimes putting them in a rocking-chair and letting them rock gently, for gradually increasing periods, is of help for contracture of the muscles of the leg. Massage may be steadily used. Extension is sometimes

useful for flexion of the knees, and gentle forcible straightening of the fingers, with the use of splints, often helps deformity of the hands. In some cases surgical measures are of value. In deciding as to these it is important to study the *x*-ray plates and determine how much damage has been done to the articular surfaces. If these show little change and the joint has become stiff, *brisement forcé* under anæsthesia is often advisable, but the joint must not be left immobile. Passive motion should be begun within twenty-four hours and active motion soon after. If the joint is put up in plaster for a week, as is often done, no benefit will result. Contracted tendons may be divided and the limb straightened. If this is done the joint should not be left in a plaster cast for some time, but passive movements should be begun early. In the knee-joint the injection of oil into the cavity is sometimes of great assistance in aiding an increase of movement. Excision of a joint may be advisable, as when one knee is markedly contracted and the other in fair condition. With marked proliferation of the synovial membrane of the knee-joint incision and removal of the hypertrophied villi may give much improvement.

It is well to try and get these patients going about as much as possible—at first with assistance and crutches, then with the crutches themselves, and later with one crutch and a cane.

Villous Arthritis.—This may demand special treatment by bandages or apparatus, but if these do not aid it may be well to advise surgical measures. As a rule, removal of the hypertrophied fringes gives great relief and improved function of the joint.

Atrophic Form.—So far as regards treatment this is the most unsatisfactory form, as it is too often progressive despite all treatment. Every effort should be made to keep up the general health by diet, hygiene, etc. With the destruction of the cartilages and marked thinning of the bones, use should be somewhat restricted for a time, but some of them seem to be better with moderate use. Every patient must be carefully studied in regard to this, and while it is difficult to lay down any definite rules, generally if there is any doubt it is better to incline to rest. Hyperæmia, very gentle massage, and baking help the patient's comfort, and should be tried. Very often a change to a dry, equable climate gives good results.

Hypertrophic Form.—In this the matter of rest is important during the acute stages, when, as a rule, exercise is harmful and rest is useful. The affected joint is usually helped by some protection. Sometimes one has to take a middle course, as in the elderly patients with hypertrophic changes especially in the hip-joint. If they walk too much, there is apparently danger of stirring up the process and making it more acute; if they keep too much at rest, there may be danger of fixation. Going up and down stairs is often especially harmful to them. With overgrowth of bone it is evident that harm may be done by active or passive motion. Rest may often be secured by mechanical support, which may be useful even when it does not secure complete fixation, although the latter is usually advisable in very acute conditions.

(*a*) *Heberden's Nodes.*—These sometimes require treatment, although nothing can be done to prevent their appearance. Increase in size is often due to trauma or irritation by use, rubbing, etc., so that the patients should be especially warned against injury, and if acute features are present, such as pain and redness, they should be carefully guarded against any trauma

and kept as undisturbed as possible. If there be pain and tenderness, the most efficient treatment is usually hydrotherapy in the form of wet compresses covered with some form of protective, put on at night and left until morning. The patients should be cautioned not to rub the joints, and to limit their movements as much as possible.

(*b*) *Spondylitis with Hypertrophic Changes.*—Rest is usually the greatest aid in treatment. To secure this, a plaster jacket or some form of apparatus should be worn. Not infrequently this causes increased pain for a few days, and may have to be changed, but relief usually comes in a short time. The jacket should come up to the shoulders and well down over the hips. Some patients are relieved by a form of corset, carefully adjusted, or by a belt made of webbing. These are generally advisable after the acute stage is over. Caution should always be given as regards the danger of trauma or strain. Lifting of weights or severe exertion, especially in strained positions, in fact anything which may throw a sudden strain on the spine and its muscles, should be carefully avoided. In the patients who suffer especially when in bed, care in the kind of mattress, adjustment of small pillows, etc., may be of use. In the patients who have a general process which is recognized early, an attempt may be made to have the spine in the most favorable position before fixation occurs. They are usually better off if this occurs in as upright a position as possible and by attention to this something may be done to lessen the marked bowing, with the convexity backward, which compels the patient to walk with the head forward and the eyes looking downward.

In the more generalized forms it is well to save the joints during the acute stages. This is not necessarily always complete fixation, but certainly excessive or even normal use should be avoided. After the acute features are over, such a joint as the knee is often helped by some support, such as an elastic covering. If bony exostoses are causing mechanical difficulty, surgical measures may give some relief; bony spurs may be removed or the osteophytes about the joint (*e. g.*, around the acetabulum of the hip-joint).

In all forms attention should be paid to associated conditions, such as flat foot, knock-knee, etc. The use of weights may relieve deformities greatly. In regard to this the orthopædic surgeons have done much to aid these patients.

Vaccines.—If we are correct in supposing that an infectious process of some kind is the important etiological factor, the hope is suggested that by the means of vaccines some help might be given. Thus far this has not proved to be the case. It is rarely possible to determine the causal organism. When this can be done the use of vaccines is well worth a trial.

In conclusion, emphasis should be laid on the need of perseverance and patience in treating patients with these chronic joint conditions. Early recognition, persistent and intelligent fighting, and hard work often accomplish wonders.

MYALGIA.

Under this term or the unsuitable one of "muscular rheumatism" are grouped a variety of conditions but little understood and which have perhaps in common only the symptom of pain. These are comparatively frequent in occurrence, vary greatly in severity and acuteness, and for the present have to be regarded as difficult of explanation. The acute forms we see especially

as torticollis or lumbago. The more chronic forms are associated with more or less pain and at times with varying degrees of disability and stiffness. The essential nature of the condition is in doubt. By many it is regarded as associated with rheumatic fever, or being a manifestation of the rheumatic state. Others regard it more in the nature of a neuralgia, some as connected with a diathesis or gout. The changes are apparently very largely in the white fibrous tissue, consequently the tendons, muscle and nerve sheaths, periosteum, the various fascia, and the fibrous portions of the ligaments are involved. Consequently, for many of this group the designation fibrositis might well be used.

The *etiology* probably differs in the acute and chronic forms. The acute form occurs more often in men and in adult age. It may follow exposure to cold, as seen especially in torticollis, but here, as in other forms, trauma often plays a part. Thus, in the production of torticollis, if a patient is lying with the head in a bent position the condition is apparently more likely to develop. It is, however, especially in the production of lumbago that trauma seems to be important. Some strain, as in lifting or working in a bent position, is a common contributing factor. This, with exposure, is a common cause in laboring men. The more chronic forms are commoner later on in life and occupations involving exposure are apparently important factors. In both the acute and chronic forms one attack seems to predispose to another. There is an impression that members of rheumatic families are more prone to the disorder. The same is said of gout, but it is difficult to be certain exactly what condition we are dealing with in this case.

The essential pathological lesions are, as already said, apparently in the white fibrous tissue, and the condition is probably of an inflammatory nature. There is a serous exudation in the affected parts, which later may be followed by proliferation of the fibrous tissue. This may be absorbed entirely, but if long continued will be more or less permanent and may extend over a considerable area. As a result of these, various nodules have been described, the histological character of which has been described by Stockman. Thus, in one patient a small nodular swelling in the buttock was excised, and found to consist of a portion of the perimysium of the gluteus medius muscle. Sections showed it to consist of the fibrous sheath of the muscle hypertrophied and œdematous. In place of the fiber, tissue penetrated between the muscle fibers, some of which were degenerated. The small vessels showed periarteritis and endarteritis. There was no evidence of any very acute inflammatory reaction and no organisms were found in the tissues.

Changes in the Joints.—Certain of these have been described under the heading of Chronic Rheumatism, but it is a question whether such cases do not more properly belong under the heading of Arthritis Deformans. As a result of the thickening of the muscle sheaths a considerable degree of disability may be produced, following which there may be quite marked muscular atrophy and a certain amount of contraction.

It is probable that a number of factors enter into the production of this condition. The changes described by Stockman suggest either chronic low-grade infection or the influence of toxins. The condition in some ways is not unlike that which we find in the synovial membranes of the joints in some cases of arthritis deformans. In the forms occurring in more advanced life, there is perhaps a greater tendency to degenerative changes, and probably the effect of wear and tear has to be taken into account as well.

As to the *symptoms*, in the *acute* form the main features are pain and disability often coming on suddenly. The pain may be sharp and fairly constant or dull, and becoming severe on movement, or when the muscles are placed in certain positions. Thus, in torticollis any attempt to straighten the head may cause severe pain. Special features depend on the locality affected and certain forms are fairly well recognized.

1. Torticollis affects the muscles of the neck laterally or posteriorly. The pain is generally very severe, and the patient holds the head to one side. The condition is usually unilateral. It may persist for a few hours only or for several days.

2. Lumbago affects the muscles of the back. The onset is usually sudden, and often after some muscular effort which involved bending or lifting. The pain may only be present on movement, but is sometimes so severe as to incapacitate the patient and prevent any movement. The duration is very variable, but is usually a few days. Some individuals have regularly recurring attacks. As with torticollis, a striking feature is the frequent prompt response—although the effect is usually only temporary—to local counter-irritation.

3. Pleurodynia involves the intercostal muscles and sometimes the pectoralis and serratus muscles. The pain is severe and greatly aggravated by any movements. The respiratory movements are restricted on the affected side. Pressure may cause severe pain.

4. Various other forms are described as *scapulodynia, dorsodynia*, etc. Their general features are much the same. A certain set of muscles may apparently show a tendency to repeated attacks.

Constitutional symptoms are not common. Fever is rare and the pulse rate is not increased.

The *chronic* forms are distinguished especially by aching, soreness, or pain, and varying disability which consists chiefly in stiffness and inability to perform certain movements. These may be more or less constant, or come and go for various periods. In severe cases they are present constantly, and exacerbations occur, as, for instance, after exposure. Sudden muscular movements are especially apt to cause pain. In addition there may be severe pains which are apparently neuralgic in character.

The muscles may be tender on pressure, and in some cases definite areas of induration may be felt. Stockman lays considerable stress on these, and describes some as being soft and ill-defined, while others are firmer. They are usually tender on pressure. He describes the commonest seats as the lumbar aponeurosis, the calves, fascia lata, trapezia, insertion of the deltoid, the biceps, the intercostal and pectoral muscles, the glutei and soles of the feet. With time, considerable disability and marked loss of function may result.

The recognition of this condition, as a rule, does not offer much difficulty, with the exception of lumbago. Here the possibility of arthritis of the spine, sacro-iliac-joint diseases, tuberculous disease of the spine, or secondary malignant growth in the spine must be kept in mind. Careful examination with the possibility of these kept in view and the need of excluding them before a diagnosis of lumbago is made, are the most important points.

Concerning *treatment*, as regards the general management, it is usually well to open the bowels thoroughly and to see that the patients take large amounts of water—that any particular kind of water has any special effect is doubtful. For the improvement of the pain some of the salicylate prepara-

tions are generally most efficacious. Sodium salicylate, in doses of gr. x to xv (gm. 0.6 to 1), or aspirin, in gr. x (gm. 0.6) doses, may be given. For some patients small doses of colchicum are most useful. Guaiacum and potassium iodide give considerable relief in some instances. As to local measures, the most important is rest to the affected muscles. This may be secured by mechanical means, especially strapping. It is probable that the often used plaster, especially to the back, acts in this way as much as any other. Local counterirritation is particularly helpful. The Pacquelin cautery may be applied or blisters used. Acupuncture is very helpful in lumbago; either sterilized needles or hatpins are inserted in the lumbar muscles, after cleaning the skin, and left there for five minutes. In some cases the use of the constant current is very helpful. In those subject to repeated attacks, every care should be taken to avoid the exciting cause, which in many patients is exposure to cold. Some of those who are susceptible find that a Turkish bath taken at the very onset frequently has a marked effect in limiting the progress.

CHAPTER XXII.

OSTEOMALACIA.

By GEORGE DOCK, M.D.

Synonyms.—Mollities ossium; fragilitas ossium; ostitis malacissans; malacosteon; halisteresis ossium; Osteomalacie (German); ramolissement des os, ostéomalacie (French); rammolimento delle osse (Italian).

Definition.—A chronic disease characterized by pain and muscular weakness, and by decalcification and absorption of bones already formed, with bending or fracture, and consequent deformity.

History.—Softening of the bones was noticed by medical writers from an early period, but its accurate study began with the work of Glisson on rickets (1650), and ever since that time the two diseases have often been compared and contrasted. In the early literature only the most extreme cases were described, as in the works of Duverney (1751) and Morand (1752). Levacheur (1772) pointed out the relation of osteomalacia to pregnancy. Lobstein and Guerin indicated the anatomical features more closely than had their predecessors, and Kilian (1829) introduced the terms "cerea," *seu* "flexilis," and "fracturosa" to signify two marked characteristics of the affected bones. Important contributions were made later by Virchow, von Recklinghausen, Pommer (1885), and Gelpke (1891). A new period was introduced by Fehling, with his ovarian theory of the disease, and with the investigations of Latzko, Hoennicke, Erdheim, and others an era of most promising clinical and anatomical investigation has begun.

Extent and Geographical Distribution.—Osteomalacia has been considered rare everywhere, but with the more accurate recognition of its symptoms this has been changed, although it is too early to speak positively of the existence or absence of the disease, which should be more carefully looked for in all parts of the world. It will probably be found that mild cases occur in many places, but the existence of certain severe foci will probably not be less striking than it now appears. These foci are in Italy, especially the Valley of Olona, near Milan, and Calabria; in Switzerland, especially the Ergolzthal, near Basel, and various parts of the Rhine country, South Germany, and Austria. England, Northern Europe, the Balkan countries, and America seem relatively free.

Etiology.—The explanation of the endemic occurrence of osteomalacia was naturally sought in the soil and water, but with contradictory results. By feeding animals with hay from endemic foci Roloff was able to cause characteristic changes of bones. In some endemic areas the water is relatively rich, in others poor, in lime. Areas at one time affected have become relatively free from the disease, *e. g.*, East Flanders.

Unfavorable hygienic surroundings in the dwelling house or work place, dampness, insufficient clothing, trauma, psychic shocks, and poor food, as

sour rye, have all been looked upon as causes, but they obviously can be concerned only in an indirect way. The majority of patients belong to the poorer classes, but there are exceptions.

Sex.—Women show a remarkable predisposition to osteomalacia. Among older statistics a proportion of ten to one was general. Latzko more recently (1897) found 5 men among 120 cases. The difference cannot be explained by the influence of pregnancy, as women who have not borne children are also more disposed to the disease than men. It probably is related to the function of ovulation.

A relation between osteomalacia and pregnancy, the puerperal state and lactation can be seen not only in the human species, but also among lower animals (cattle, sheep). Multipara and especially those with rapidly following pregnancies are more disposed than others. The tendency to dental caries, to slow callus formation after fracture, and the craving for earthy substances, so often noted in pregnancy, may be looked upon as having some relation to the greater incidence of osteomalacia. The belief that osteomalacia occurs chiefly in women of unusual fertility is based upon a statistical error. Heredity plays no part; a family tendency has rarely been observed. The true relation of osteomalacia to rickets is not known. They occur together in certain localities, but considering the frequency of rickets this is not remarkable.

Age.—The majority of cases begin between the twentieth and thirtieth years. Cases before twenty are rare, but Drake reports the case of a Brahmin, married at eleven, pregnant at fourteen, and with severe osteomalacia at eighteen. The observations of von Recklinghausen, Rehn, and Juergens make it probable that osteomalacia can occur in childhood, distinct from rachitis, or even *in utero*. It may be combined with rickets. Ziegler denied the non-rachitic nature of the changes in one of von Recklinghausen's cases. Juvenile and virile rickets sometimes follow trauma and infectious diseases. Langendorff and Mommsen[1] report an interesting case. Senile osteomalacia is rare. Pierart, out of 247 cases, found only 22 above the age of forty-five. The symptoms may be misleading and diagnosis impossible, as in virile osteomalacia. In the case of Davis,[2] a man, aged thirty-three years, had complained of weakness and pain in the upper extremities for a year, and fractured the left arm by a fall. There was no union. Exploration led to a diagnosis of sarcoma by examination of tissue from the seat of fracture. Careful differential diagnosis seemed to confirm this, and the arm was removed at the shoulder. Skiagrams had been made, but were unsatisfactory. The later examination showed the process was osteomalacia.

Pathology.—There is no unanimity regarding the pathology of osteomalacia, and many facts point to a variety of causes and modes.

An important suggestion grows out of the observation of Hanau on "physiological osteomalacia," a porosity of bone not infrequently found, especially in the pelvic bones, in pregnant women. From this it would seem an easy step to the pathological osteomalacia of pregnancy and lactation, and especially when we consider the need on the part of the growing infant for lime and phosphorus and its supply in the milk. The hyperæmia

[1] *Virchow's Archiv*, 1877, Band lxix.
[2] *Annals of Surgery*, 1904, xl, 225.

of the bones of the pelvis during pregnancy, the changes that occur in the bone marrow, the remissions of the disease during menstruation and relapses in new pregnancies, all go far to indicate a close relation of osteomalacia to the genital functions of the female. Fehling's brilliant hypothesis, that the disease is due to a morbid activity of the ovaries, leading to passive hyperæmia and absorption of lime, has in so many cases been confirmed by the effects of oöphorectomy, that it must be considered as partly, at least, applicable. On the other hand, it is negatived by many cases of failure to recover after operation, by relapses, and by improvement following Cæsarean section, or even anæsthesia. Latzko saw chloroform anæsthesia followed by temporary improvement in ten cases. On the other hand, improvement has followed in cases of oöphorectomy under ether and under local anæsthesia. Cases of infantile and senile osteomalacia, as well as cases in men, are not to be explained on the ovarian theory, which, of course, still leaves to be explained the remarkable geographical conditions.

The nervous-metabolic theory of Pommer, though somewhat strengthened by more recent observations on the trophic disturbances of bones, and the theory of Comby, of nutritive disturbances of bone by fermentation products from a dilated stomach, cannot be generally applied.

E. Hoennicke[1] has advanced a thyroid theory, based on many facts relating to the thyroid gland and its functions. He saw a case of osteomalacia in a man, aged forty-seven years, who also had exophthalmic goitre. Similar cases have been reported by others. Hoennicke shows a close relation geographically between osteomalacia and goitre; he found an association of goitre in a considerable number of cases of osteomalacia, and he points out the well-known trophic and metabolic relations of the thyroid to the bones, and the mutual relations of the thyroid and ovaries.

Erdheim[2] calls attention to the relation between lime metabolism and the parathyroid bodies and its possible bearing on osteomalacia. On examining the parathyroids from eight cases of puerperal osteomalacia he found evidences of hyperplasia, followed by atrophy and small-cell infiltration. The occurrence of tetany in osteomalacia adds interest to the observation, and, as Erdheim points out, suggests that the parathyroid hyperplasia in osteomalacia may be due to an increased demand upon the glandular function on account of toxic substances produced in the ovaries or some other organ. The subject is obviously one of the greatest importance, and the exact condition of the parathyroids must be investigated in all future cases of osteomalacia.

A theory that need only be named on account of its historical interest, but has long since been abandoned, is the acid theory. According to this, first lactic acid, later oxalic, formic, carbonic, and nitric acids, were supposed to occur in the blood. Sometimes they were detected in the urine. Observation showed the facts to be susceptible of different interpretation and incapable of explaining the disease. The same may be said of the grape-sugar theory and that of diminished alkalinity of the blood.

Infection has been asserted to be the cause by many authors, and seems highly probable, but positive evidence is not yet available. The occurrence

[1] *Ueber das Wesen der Osteomalacie*, Halle, 1905.

[2] *Ueber Epithelkoperbefunde bei Osteomalacie, Sitzungsbericht der kais. Akad. der Wissens. in Wien, Math.-naturw. Klasse*, 1907, Band cxvi, Abt. III.

in the previous histories of severe infectious diseases, such as puerperal, typhoid, and scarlet fever, pneumonia, syphilis and gonorrhœa, and the frequent relation of such infections to the bone marrow, are suggestive.

Laufer,[1] in a valuable study of the subject, suggests the following as a working theory: Osteomalacia can be looked upon as a degenerative disturbance of nutrition in the bones, in the general sense that all degenerative nutritional disturbances are characterized frequently by diminution or disappearance of tissue and by diminution of function. Etiologically, it may be supposed that various obscure factors—improper or insufficient food, trauma, repeated pregnancies, etc.—cause retrogressive changes in the bones. The changes in the bones, decalcification and new formation, are very characteristic of bone physiology, as seen after fractures, and are at first reparable, but continued action of the noxa or other unfavorable conditions permit the characteristic changes of osteomalacia, that may be looked upon as a dystrophy peculiar to the osseous system. The possibility of recovery under various conditions leads us to suppose the dystrophy is independent of irreparable lesions of bones.

The *bones* in osteomalacia, as the name signifies, are soft. At autopsy they can be squeezed or twisted, sometimes feel like wet paper, and cut without resistance. They look and feel greasy. The difference between the brittle and yielding ("waxy") varieties is unimportant. On section the bone tissue proper is much reduced, both in the compact and spongy part. The bones are often altered in shape, generally or in part. There are often cystic cavities of various sizes in the bones, containing clear or yellow or red serous fluid, or dark masses of more or less altered blood. The marrow is yellow and fatty for the most part, sometimes hyperæmic or lymphoid in appearance. In some places only the periosteum preserves the original shape of the bone. The periosteum is often thick, hyperæmic, and in stripping shows the surface of the bone rough, the Haversian canals sometimes wide and filled with serous fluid. In consequence of the loss of bone tissue the specific gravity is much reduced, from 1.877 to as low as 0.721. The bones permit the passage of Röntgen rays with unusual ease, depending on their decreased density. The process of absorption begins in the marrow cavity and extends outward.

Microscopically, besides the increased sponginess or actual loss of bone tissue, there is often a border of osteoid tissue along the bone. From the fact that this stains red with carmine it has been called the "carmine border." This is recognized as decalcified bone, as von Recklinghausen set forth. The margin of normal bone is not even or systematic, but very often forms a zigzag or irregular line. The decalcified parts at first contain canaliculi and lamellæ, and show at the margins between the calcified and non-calcified parts characteristic lattice-like figures, due to the presence of air in the canaliculi and the spaces occupied by the bone corpuscles and their processes. Hanau's view, that the lattice figures may correspond to defective calcification has not been verified by others. The decalcified parts become softened, sometimes fibrous, like asbestos, sometimes absorbed, leaving spaces filled with marrow, or with mucoid or granular material. Newly formed bone tissue is deposited in various parts, but in general in small amounts, so that production is never relatively or absolutely important. The marrow is

[1] *Centralblatt für die Grenzgebiete der Med. und Chir.*, 1900.

either fatty or lymphoid, and with giant cells and osteoblasts in varying proportions. Hemorrhages and pigmentation from old hemorrhages cause a great variety of color and of microscopic structure. In some areas the marrow is gelatinous or even watery. The softening, and especially the irregular and large cystic areas of decalcification, explain the more striking deformities that occur in the disease.

The bones most affected are those of the pelvis. The sacrum is pushed forward and downward, the posterior parts of the iliac bones with it, while the acetabula are pushed up and inward by the heads of the femurs, the symphysis being squeezed forward like a beak. Other deformities in the shape and position of the pelvis depend upon the position in which the patient remains. The most extreme deformity gives the pelvic cavity the shape of a clover leaf or a Y. In patients who remain long on their backs the pelvis is flattened from before backward. The narrowing does not always act as an obstruction to delivery, as the bones are sometimes elastic ("rubber-pelvis"). Hugenberger thinks that such cases occur in 30 per cent. of osteomalacia. Casati, out of 42 cases, was obliged to do Cæsarean section only twice, and Fehling advised delay in operating for similar reasons.

Vertebræ.—The normal curves are exaggerated, especially in the cervical part, so that the chin may rest upon the sternum. Lateral curvatures are frequent, but vary with the habitual position of the patient. Pregnancy often causes the most pronounced deformities. The whole vertebral column is shortened, especially in the lumbar portion. The body sometimes shows a constriction and duplication at the waist, as if the parts had been telescoped.

The ribs are often broken from muscular action, in breathing, or from pressure. They may in part overlie each other. The sternum is often curved or bent. The thorax in general is usually compressed in various directions, causing in time displacements of the heart and lungs, with dyspnœa, asthmatic attacks, and palpitation.

The long bones of the extremities are affected late in most cases, but may be early, causing spontaneous fractures, with sometimes large but usually imperfect callus, or leading to coxa vara, genu valgum, or flat foot. The cranium is rarely affected.

Litzmann has made the following table of the relative frequency of the affection of various bones:

	Puerperal.	Non-puerperal.
Pelvis	82	40
Vertebræ	46	40
Thorax	26	37
Lower extremities	15	36
Upper extremities	10	30
Head	7	24

The joints are not affected. The muscles are atrophied and degenerated, sometimes to a remarkable degree. The nerves of the extremities were also found degenerated by Schlesinger.

The ovaries show no constant change. Fehling, who first attracted attention to the ovaries, described hyperæmia, but Winckel and others attributed that to accompanying malpositions. Fehling and others also described hyaline degeneration of stroma, follicles, and bloodvessels, but without proving any or all of the changes are characteristic of or peculiar to osteomalacia.

The thyroid is often enlarged, and postmortem shows various goitrous changes. The work of Hoennicke, mentioned above, should be consulted in reference to the thyroid, and the work of Erdheim in regard to the parathyroid.

Symptoms.—The beginning of osteomalacia is usually impossible to recognize. Sometimes the increase of symptoms during pregnancy or the puerperal period permits a relatively easy diagnosis, but in most cases the disease is far advanced before any suspicion of its existence is entertained. The rarity of the disease has much to do with the present condition of diagnosis, and a knowledge of the early symptoms and a keener search would result in the more frequent discovery of mild cases.

The earliest symptom is pain. This is usually called rheumatic, but varies in character from dull to neuralgic. In pregnant women it is often felt in the pelvis, especially the sacral region; in others in the thorax, back, or one or more extremities. Movement, but also remaining quiet for a long time, is likely to increase it. The pain is often spontaneous, sometimes nocturnal, but can usually be provoked by pressure on certain bones, especially the pelvis and vertebræ. Tenderness over nerve trunks is sometimes present. Girdle pain has been noted. With the pain there is usually a feeling of weakness and often a subjective and objective stiffness, with contracture or spasm of certain muscles, as the ileopsoas (Renz and Koppen) or the adductors of the thighs (Latzko). From various causes the gait becomes waddling and uncertain; the body sometimes leans forward. Sometimes the gait is spastic, and then the patellar reflexes are usually increased, and there may be intention tremor. If at the same time there is paræsthesia, an erroneous diagnosis can easily be made.

If the patient is examined at this time, naked, as is necessary in order to avoid error in all suspected diseases of the motor apparatus, it may be found that besides confirming the statement of the patient or friends that she is shorter, some distinct deformity can be detected. There may be lordosis, or other curvature of the vertebræ, or change in the shape of the thorax, or a furrow in the lumbar region, or a change in the position of the hips and the shape of the symphysis pubis. The linea innominata may be straightened, the diameters of the pelvis altered, but with the conjugata vera little or not at all lessened. Examination of the muscles often reveals tremor, fibrillary or gross, or spasm or contracture. Paræsthesia in some cases, especially in the legs, and with other nervous symptoms may be due to alterations in nerve trunks from the deformity of the spine and pelvis.

The digestive functions in the early stages are usually not affected. Menstruation and conception are often normal. The difficulties of confinement need not be described here, but it may be pointed out that the fear of conception is not now so great as it has been in the case of osteomalacia patients.

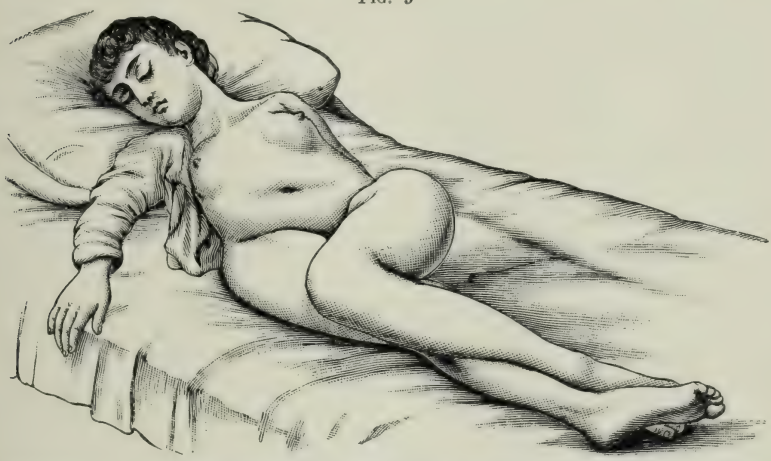
The blood shows no characteristic changes. It becomes chloranæmic, with reduction of both coloring matter and number of red cells. The eosinophile cells are sometimes slightly increased, sometimes diminished or absent. Lymphocytes vary; sometimes the large forms are increased. Myelocytes sometimes occur. An increase of the resistance of the red cells has been asserted. The alkalinity of the blood is not always diminished; it may even be increased.

The urine often contains excessive amounts of calcium and phosphates, but these vary without distinct relation to the clinical features. Lactic

acid is rarely present, and not characteristic. Bence Jones albumose was first found in a case of (probable) myeloma, erroneously called osteomalacia. Since then it has often been found in cases of myeloma. In Dock's case it was found, without other explanation than the osteomalacia.

The general and proteid *metabolism* in osteomalacia are not altered except as the result of associated conditions. The bones become poorer in calcium and other mineral constituents, especially calcium phosphate, and richer in organic matter, especially fat. The earlier statements regarding lactic acid in the bones are now known to be erroneous. The lime leaves the body through the kidneys and intestines. Phosphate calculi are important factors in the urinary excretion. Excretion and retention of calcium and phosphates vary, however, even without treatment, and no conclusion regarding the process in the bones can be drawn from the condition of the urine.

FIG. 9



Osteomalacia. The photograph of a patient whose case was reported by the author. (*American Journal of the Medical Sciences*, 1895, cix, 499.)

In the further course of the disease deformities of all the affected bones become most pronounced, and the body assumes the most bizarre attitudes. The skin becomes sallow and flabby. The muscles waste, fractures and callus may add to the deformity. Œdema, dyspnœa, palpitation of the heart, fever, and sweats may be present in various degrees and combinations. Bronchitis and bedsores indicate the extreme cachexia. Dysuria is a frequent symptom. Renal calculi may be passed in large numbers and cause intense agony.

There are many *varieties* of osteomalacia. In rare cases it runs a rapid course, a year or less. In most the course extends over five, ten, or more years, and in this time remissions may occur, lasting many months or years, or recovery may ensue at any time under treatment, rarely spontaneously. Although pregnancy and even menstruation usually make the symptoms worse, improvement or even recovery has been observed in the former. Death is usually due to exhaustion, cardiac weakness, bronchopneumonia, or some other infection. Bedsores often influence the exhaustion and infection.

Diagnosis.—In the early stages the differential diagnosis cannot often be positive, even in an endemic focus. The rheumatic or hemorrhoidal pains of pregnancy must be excluded by careful examination of their seat and course, and the presence or absence of bone tenderness. Later, lateral sclerosis, transverse myelitis, polyneuritis, tabes, multiple myeloma, carcinoma, sarcoma, tuberculosis, osteitis deformans, senile osteoporosis, sometimes arthritis deformans, must be excluded.

It is not necessary to speak in detail of each possibility. Only complete and usually repeated examination can prevent error. Multiple myeloma can probably not be positively differentiated in all cases. Coxa vara, genu valgum, or rupture of pelvic articulations may have to be considered. Hysteria sometimes causes a striking simulation of osteomalacia. The differentiation of late rickets and osteomalacia depends upon the presence or absence of the rachitic epiphyseal changes, the less severe pain, and the tendency to cranial changes. Skiagraphic examination will often be of value. In some cases the results of treatment may throw light on the diagnosis.

Treatment.—**Prophylaxis.**—Gross errors in hygiene are important to correct in all endemic foci of disease, or in an individual case. This is especially important in the latter in periods of remission or after recovery. Fresh air, good food, exercise, and bathing are all useful. Nursing must not be permitted to an osteomalacic mother.

Diet.—Substances containing considerable lime and phosphorus should be preferred, such as milk, eggs, fresh meat, fish, beans, peas, and cereals.

Drugs.—Lime has been recommended, but is useless theoretically and has failed in practice. Calcium phosphate is but little better. The most useful drug is phosphorus, which is recommended by all who have used it persistently in large doses. It is given most frequently in cod-liver oil, in solutions of 0.06, 0.08, or 0.1 to 100. A teaspoonful of this is to be taken once daily, or 3 to 5 mg. (grain $\frac{1}{20}$ to $\frac{1}{12}$) at each dose. If cod-liver oil is not well borne, almond oil can be used, as in the Oleum phosphoratum of the British Pharmacopœia. It can also be taken in pills (Pil. Phosphori, U. S. P.) containing 0.6 milligram (grain $\frac{1}{100}$) each. The treatment must be continued at least one or two months. Improvement may not be apparent for three or four weeks. Kozminski recommends prolonged intermittent treatment based on the bone symptoms. Sternberg has given as much as 2.25 grams of phosphorus without toxic symptoms. The taste of phosphorus may be avoided by chewing orange peel or coffee beans.

Phosphorus is slower and less certain, but safer than castration, the application of which we owe to Porro, who in 1878 reported a case of osteomalacia that recovered following the operation named after him. Fochier and Levy thought sterilization was the cause of the recovery. Fehling (1886) showed the value of removal of the ovaries, and developed the theory already mentioned. While the theory is not accepted, the beneficial results of operation cannot be questioned, and although efforts have been made to attribute the recovery either to the narcosis or the operation *per se*, they have not been successful. The results of castration are sometimes remarkable. Pain sometimes disappears in a few days. But the improvement is neither uniform nor permanent, and phosphorus treatment may be carried out after it with advantage.

The indications have been formulated by von Winckel and others as follows: (1) Castration is indicated when other methods of treatment have

failed and softening of the bones has advanced so far that life is endangered, or if the condition is such that death may occur before medicinal treatment can have an effect. (2) It is indicated in patients with pelves so narrow that pregnancy would necessitate Cæsarean section, and in case Cæsarean section is necessary.

Senator has used oöphorin with good results, but others (Latzko, Schnitzler, Bernstein) who have tried the method have failed. Bossi has advocated the use of adrenal preparations subcutaneously. There is an error regarding dosage in Bossi's publications, but he apparently used the material to the point of tolerance, as shown by chills, tremor, a feeling of suffocation, and a sense of constriction behind the sternum, coming on soon after the injections and lasting about a half hour. The symptoms increase with the number of injections. Besides Bossi, Ruffi, Tanturri, and Reinhardt had favorable cases, but others have failed.[1] Hoffmann has used the serum of thyroidectomized sheep and reports improvement in two months.

In a disease like osteomalacia any treatment based upon probable causes seems legitimate, but the chronic and variable course of the disease suggests the value of caution in announcing results.

Symptomatic Treatment.—In all cases various symptoms are certain to demand treatment. Comfort, the relief of pain, and the diminished danger of fractures should be provided for by a proper bed and care in moving or being moved. The skin requires care at all times, and especially if bedsores threaten or occur. The bed pan and urinal must be used. Pain in the muscles and cramps should be relieved by hot baths, massage, fomentations, or at last morphine. Wine of colchicum seeds has been used by many with apparent advantage for the rheumatic pain. Diarrhœa and constipation must be treated as in other diseases.

[1] See the review of R. de Bovis, *La Semaine Médicale*, 1908, p. 241.

CHAPTER XXIII.

ASTASIA-ABASIA. ADIPOSIS DOLOROSA.

By DANIEL J. McCARTHY, M.D.

ASTASIA-ABASIA.

Definition.—A functional disturbance of the neuromuscular mechanism first described by Blocq in 1888 as a morbid state "in which the impossibility of standing erect and walking normally is in contrast with the integrity of sensation, of muscular strength, and of coördination of the movements of the lower extremities."

Etiology.—The disease is not an uncommon complication, and in reality a symptom-group of the functional neuroses—hysteria, neurasthenia, epilepsy, chorea, etc. While it may occur at any age, it is more frequently met with in youth and early adult life. Knapp's statistics of 50 collected cases show an equal number in men and women. Of these cases, 21 showed hysteria, 3 chorea, 2 epilepsy, and 4 intention psychoses. It may develop spontaneously or during the course of one of the functional neuroses; emotional excitement, traumatism, or exhaustion may be determining factors. It has been noted as a symptom in one case of cerebral tumor localized to the prefrontal area. It is, however, not a symptom of cerebral tumor, and must be considered in this isolated case as an accidental complication.

The absence of any causative pathology even in cases which have existed over a long period of time, the rapid disappearance of the symptoms by suggestion and other methods of treatment, the frequency of its occurrence as the complication of a functional neurosis, places it as a symptom group of a purely functional nature. The importance that has been given to it in medical literature, and the extremely puzzling clinical picture often presented have led us here, as in the other text-books, to a special consideration of the subject. There is a general tendency to consider the condition as one of pure hysteria. It may, however, exist without other hysterical stigmata, and in some cases at least, is the manifestation of the extreme fatigue of neurasthenia and negativism of some of the psychoses.

Symptoms.—In the simplest form the patient is unable either to stand or to walk and in some cases even to sit (Akathisie), and yet in the recumbent posture retains full power and coördination of all muscles necessary for locomotion. A careful examination in such cases will not show any loss of power, the sensation may be normal, the reflexes show no evidence of organic disease, the bladder and rectal functions are retained, and an examination of the cranial nerves reveals nothing abnormal. It is not at all surprising, however, that in such cases evidence of hysteria in the field of sensation and the special senses should be present. When the condition develops upon a basis of neurasthenia, marked fatigue and quickened reflexes with paræsthesia are to be expected.

Apart from the typical and complete case, there is a large group of cases in which the ability to stand and to walk is not entirely lost, but interfered with to a greater or less degree, as is shown by a sudden or general loss of power with incoördination. The incoördination in these cases is of an irregular type, and can be easily distinguished from the ataxic gait of the tabetic or that seen in cerebellar disease. Even in cases which show a complete loss of the ability to stand or walk the patients are still able to walk on all-fours, to walk backward, and in some cases to swim (Oppenheim).

The fatigue consequent upon muscular exertion, seen in neurasthenia, may, in some cases, be so intense as to constitute the basis for the loss of power, accentuated and to a certain extent determined by the nervous excitement and lowered will-power. In other cases the disease has its origin in a psychasthenia. In an individual who has a dominating fear of paralysis, after prolonged introspection an astasia-abasia may develop upon a moderate or marked grade of fatigue. Excessive fatigue, more particularly when associated with mental stress, may be the starting point in one who is neither a psychasthenic nor an hysterical patient. In the nervous or timid child, fear of pain after a fracture or other injury to the foot may cause the condition.

Ziehen (Eulenberg's *Real-Encyclopedia*) gives the following classification:

1. Hysterical astasia-abasia dependent upon the subconscious idea implying an inability of the patient to stand or walk. He places this in the group of hysterical palsies.

2. Hypochondriacal astasia-abasia dependent upon the conscious but false idea of the inability of the patient to stand or walk. This may arise as a primary delusion or be dependent upon paræsthesia, visceral disturbance, diplopia, vertigo, cardiac palpitation, etc.

3. Affective or emotional astasia-abasia caused by a subemotional shock. An attempt to walk is associated with a sudden overwhelming fear, inhibiting the motor function.

4. The psychasthenic form of astasia-abasia dependent upon a morbid impulse or concept that develops on a false idea of inability to walk or stand, or paralysis, or a fear of falling. This form is dependent on defective will power.

Diagnosis.—Astasia-abasia must be differentiated from paralysis due to organic disease of the spinal cord, cerebellar disease, labyrinthine vertigo, and myasthenia gravis. The absence of ankle clonus or Babinski reflex, or bladder and rectal disturbance, and of sensory disturbance of organic distribution, will easily exclude organic disease of the cord. In cerebellar tumors, optic neuritis and other evidence of intracranial pressure, together with the typical ataxia, will be present. The rapid muscular fatigue seen in a myasthenia gravis after exertion may be easily mistaken for a partial form of astasia-abasia. This is more particularly true when the symptoms of the onset are most marked in the lower extremities. The loss of power in these cases is as marked, after repeated muscular exertion, when the patient is recumbent as when he is standing. The myasthenic reaction will establish the diagnosis. Intermittent claudication or intermittent paralysis of the lower extremities, due to arteriosclerosis of the vessels of these members, need only be mentioned.

Akinesia algera, a condition based upon the same neurotic basis as astasia-abasia, should be differentiated from it. In this condition, first described by Moebius, all the voluntary movements are associated with intense pain,

which increases in severity if the movements are continued. The pain may become so intense as to affect the entire body upon the slightest motion, and in this way produce a pseudoparalysis. The absence of pain in simple and uncomplicated astasia-abasia should differentiate it from the above affection.

Prognosis.—The prognosis is, as a rule, favorable. In most cases the condition yields easily to treatment. Some cases are very resistent and prolonged. The prognosis may be said to be dependent upon the underlying cause and the ease with which it may be controlled or removed.

In cases which are permitted to run for a long period of time, contractures may develop which may necessitate vigorous and even surgical treatment. The writer has seen such a case which developed on a basis of hysteria. This complication is likely to develop when the astasia-abasia is associated with a hypertension of the muscles.

Treatment.—The treatment does not differ essentially from that detailed under the functional neuroses. Removal of any causative factor which may be present, the reëstablishment of confidence, the training of the will power, and reëducation as to the method of walking, standing, etc. (following the general plan outlined by Fraenkel in tabes), are indicated. In conditions of lowered nerve tone, partial or complete rest treatment, with or without hydrotherapy, is advisable. Suggestion by means of static electricity, and in stubborn cases under hypnotism, may be necessary. It should be remembered that the cure of astasia-abasia in a patient with other symptoms of hysteria or neurasthenia is simply the relief of a symptom-group, and not the cure of the disease.

ADIPOSIS DOLOROSA (DERCUM'S DISEASE).

Historical.—A disease first described by Dercum[1] in 1888, from a case studied in the wards of the Philadelphia Hospital (Blockley). Since that time several cases from the same institution and a large number of cases from other sources have been reported.

Etiology.—It is a disease preëminently of middle life. Cases, however, have been described as early as the eleventh year and as late as the seventy-eighth year, but these are exceptions. The vast majority of cases are found in the female sex. A few cases have been reported in men, one of these by Ewald,[2] in the forty-seventh year. A history of alcoholic excess is not infrequent. Traumatism and emotional excitement have also been given as causative factors. Syphilis as a factor in the production of the disease has not been given that consideration which its frequency deserves. The disease develops, as a rule, upon a neuropathic basis, and several patients have terminated their existence in insane asylums. While heredity is not an important factor, in Cheever's[3] case the father and sister were also affected. Hammond reports two cases occurring in sisters. The majority of cases in

[1] Subcutaneous Connective Tissue Dystrophy of the Arms and Back, Associated with Symptoms Resembling Myxœdema, *University Medical Magazine*, December, 1888. See also the *American Journal of the Medical Sciences*, November, 1892, and the *Journal of Nervous and Mental Disease*, August, 1900.

[2] Ueber einen durch die Schilddrüsentherapie Fall von Myxœdema nebst Erfahrungen, etc., *Berl. klin. Woch.*, 1895, Nos. 2 and 3.

[3] *British Medical Journal*, 1904, i, 781.

women have developed at the time of the menopause or shortly afterward. One case followed an abortion, and in another pregnancy was given as the starting point of the disease.

Pathology.—To understand the position of adiposis dolorosa as a separate affection, it will be necessary to make a rapid survey of the other affections of a fatty nature. Apart from simple obesity, the following forms have been described:

1. Adiposis tuberosa simplex of Anders.[1]
2. Adiposis cerebralis.[2]
3. Adenolipomatosis.[3]
4. Multiple lipomatosis.

1. **Adiposis Tuberosa Simplex.**—This affection, at least in some of the cases, resembles adiposis dolorosa very closely. In patients who present for the most part the condition of simple obesity, Anders found localized fat tumors, sometimes painful to pressure, scattered through the abdominal fat. These differ, however, both in their formation and in their disappearance under simple dietetic and hygienic measures, from the nodules seen in adiposis dolorosa.

2. **Adiposis Cerebralis.**—This condition, described by Frohlich as dystrophia adiposo genitalis, has a very close analogy to adiposis dolorosa. In its simplest form it consists of an excessive general adiposis developing during the course of a brain tumor, which in most cases has been found at autopsy to involve the pituitary body, but which in one case was found to involve the pineal gland (Marburg). A close association has been found in this group of cases with defective development of the genital organs. Eiselsberg and Frankl-Hochwart have reported marked improvement and apparent cure after removal of a tumor of the pituitary body in one case.

3. **Symmetrical Adenolipomatosis.**—This condition, first described by MacCormac, consists of large fat masses localized to the region of the neck, the axilla, and the trunk, and associated with asthenia, mental irritability, apathy, hypochondria, enlargement of the spleen, acceleration of the pulse, and decrease of small mononuclear cells in the blood. These fat masses, even when of great size, may be associated with general emaciation. Microscopic examinations of excised portions have shown the presence of large and sclerosed lymphatic glands in the fatty tissue. An increase and diminution in the size of the fat during its development have led Launois and Bensaude[4] to consider the disease to be of lymphatic origin.

4. **Multiple Lipomatosis.**—Multiple isolated lipomatous tumors have occurred symmetrically placed in different portions of the body. On account of the symmetrical arrangement and the association of the tumors with tabes, general paralysis, sciatica, etc., it has been assumed that the nervous system and more particularly the trophic centres in the spinal cord were the cause of the affection. There is, however, practically no evidence to support such a theory. As many as two thousand of these lipomas have occurred in the same individual (Launois and Bensaude).

Careful study of the clinical and pathological features of these various

[1] *American Journal of the Medical Sciences*, 1908, cxxxv, 325.
[2] Marburg, *Wien. med. Woch.*, 1908, No. 49.
[3] MacCormac, *St. Thomas' Hospital Reports*, 1883, xiii, 287.
[4] *Nouvelle Iconographie de la Salpêtrière*, 1900, xiii, 41, 184, 243.

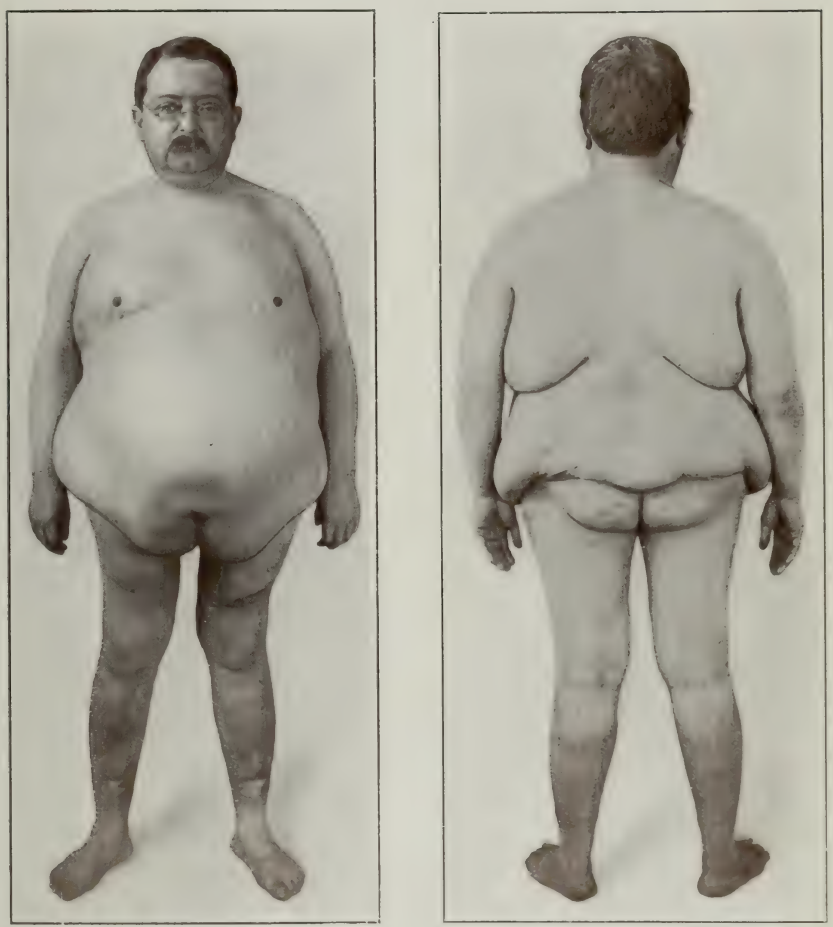
forms of diseases of the fat tissue will show a certain similarity. A study of the records of the seven cases of adiposis dolorosa that have come to autopsy has shown lesions in the thyroid gland in the nature of atrophy with compensatory hypertrophy in all seven cases. Tumors of the pituitary have been found in three cases, an interstitial neuritis in the fat tissue in two cases, and a slight sclerosis of the posterior columns of the cord in one case. In one of these cases (Dercum and McCarthy), presenting a typical clinical picture of adiposis dolorosa, a tumor of the pituitary was associated with a hypoplasia of the genital organs, extensive lymphoid infiltration of the fat and hæmolymph glands. This case forms a connecting link between adiposis dolorosa, adiposis cerebralis, and symmetrical adenolipomatosis. A recent case of adiposis, presenting clinically the picture of adenolipomatosis, in the writer's ward at the Philadelphia Hospital was found at autopsy to be a case of psammocarcinoma of the thyroid, with extensive metastasis in the fat tissue in the neck, destruction of the posterior portion of the pituitary body by an extensive multilocular cyst, sclerosis and old hemorrhagic infiltration of the adrenals, and extensive lymphadenitis with lymphoid infiltration in the fat masses, thyroid, pituitary, and adrenals.

The compensatory action of the thyroid and pituitary bodies has been demonstrated experimentally by Herring and others. It would appear from the frequency of the lesions that the thyroid was mainly at fault in the production of the disease of the fat tissue. In the case of adiposis cerebralis, the lesions of the pituitary and the improvement after the removal of the pituitary tumors would, on the other hand, point to the pituitary as the source of the trouble.

The influence of the lymphatic system must be of importance. It has been found diseased in the cases above described, and in the tumor masses excised from cases of adenolipomatosis. Virchow, in his treatise on *Tumors*, called attention to the influence of primary localized lymphadenitis on the development of the fat tumors. Dercum thought his first case to be one of a myxœdematous nature. The absence of the other symptoms of myxœdema finally excluded this diagnosis. Chipault and others have shown that localized lymph stasis may be transformed into fat tissue by a conversion of the connective tissue into fat cells. Whether the thyroid and the pituitary produce the changes above described, by disturbance of metabolism through some perturbation of the internal secretion, or whether the changes noted are secondary to changes in the lymphatic system, is a subject for further investigation.

The cause of the pain and tenderness in the fat masses in adiposis dolorosa is an interesting subject for speculation. Quite a number of the cases of adiposis dolorosa have shown some organic change in the central or peripheral nervous system. Tenderness over the nerve trunks, sensory changes, atrophy and degeneration of the muscles have been noted. Traumatism and syphilis have been noted as causative factors. Such factors acting upon the peripheral nervous system concerned with the nutritive changes in excessive adipose formation would easily produce low-grade interstitial changes in the nerves of the adipose tissue, and thereby cause the pain and tenderness. The pathological lesions of urticaria factitia described by Gilchrist present a pathological picture of transient acute inflammation. A similar lesion continued over a longer period of time and frequently repeated could easily cause the nerve changes and symptoms above noted. Such changes could

PLATE XIV



Adiposis Dolorosa. (Case of Dercum and McCarthy.)

Tumor of the pituitary body; thyroidal changes; defective development of the testicles.

From the *American Journal of the Medical Sciences*, December, 1902.

more easily be produced in nerves whose function and nutritive tone was already lowered by some metabolic or exogenous intoxication.

Symptoms.—The disease begins, as a rule, in a slow and insidious manner, in the formation of either excessive deposits of fat scattered diffusely over the trunk and extremities, or in the form of irregular deposits of fatty tumors. It may develop as an independent affection in which the adiposis constitutes the disease, or may, on the other hand, develop in one who is already of a fatty habit. The development of the disease is best studied in the latter group. A woman in middle life, of moderate obesity, develops, with or without prodromal symptoms, areas of painful swelling, irregular in size and distribution, somewhat elevated above the surrounding fat, the overlying skin of a normal appearance, slightly reddened, more often congested, and rarely with distended veins. These areas vary from one to two or four inches in diameter, are soft and somewhat œdematous to touch, exquisitely painful to palpation, and are often associated with a burning or lancinating subjective sensation of pain. After several days this condition disappears, leaving an indurated area in the fat tissue. This area from time to time is subject to a recurrence of the same condition less intensified, until finally a distinct nodular tumor formation of considerable resistance and consistence is left. This nodule is sensitive to pressure, at times even to light palpation, and constitutes the basis of the disease, adiposis dolorosa. Similar areas develop elsewhere through the fat tissue of the trunk and extremities, never affecting the face, the hands, or the feet. With further development there may or may not be an excessive deposit of fat. In the latter event the nodules may be seen distinctly elevated above the surrounding tissue, having somewhat the appearance of a multiple lipomatosis. In diffuse cases the fat is deposited in large masses, localized to certain areas, such as the abdomen, chest, thighs, etc., or massed in a general diffuse way over the entire trunk. Examination shows indurated areas, sensitive to palpation and pressure, scattered here and there throughout the fat masses. In the acute stage the swollen mass often reminds one of "caking breast." As the disease progresses to a full development, the areas of acute swelling and tenderness become less frequent, and finally disappear altogether. Nodules in the fat remain as circumscribed masses, sensitive to pressure, and associated with diffuse pain of varying character described as neuralgic, rheumatic, etc. In some cases there is no history of the acute swollen areas, but, on examination, fully developed, painful, tender masses are present. In some of the diffuse cases, folds of fat give a sensation to the touch as of a mass of worms. In some ill-defined cases, which ought not properly to be classed with this disease, the whole fat tissue is sensitive without the formation of nodular areas and without spontaneous pain.

Pain is a very prominent symptom present in all well-marked cases at some time or other, and may precede the development of the fatty nodules. It is often the only symptom complained of, and may be a sharp lancinating pain or a dull ache, and is often described by the patient as a burning pain. It does not follow the course of the nerves, and is often associated with tenderness along the nerve trunks. While the painful and tender fatty areas constitute the main and the essential symptoms, a rather wide group of associated symptoms are frequently present. The most common of these is asthenia. It is exceptional to find a well-developed case of adiposis dolorosa in which this symptom, in some grade, is missing. It may be nothing

more than the nervous apathy and sluggishness of very fat people, but in the majority of cases is so marked as to be considered of pathological origin. Psychic symptoms are not infrequent. The most common of these is a querulous irritability. Mental apathy and psychic depression are most common in the asthenic cases. Delusional states and dementia sometimes necessitate the incarceration of the patient in an asylum. In Burr's[1] case the mental symptoms were largely due to a brain tumor. The reflexes are diminished and sometimes lost, but may be increased.

In Dercum's first case there were areas of anæsthesia and hyperæsthesia, and several cases showing sensory changes have since been reported. Disturbance of the vasomotor system has been frequently noted. Variations

Fig. 10



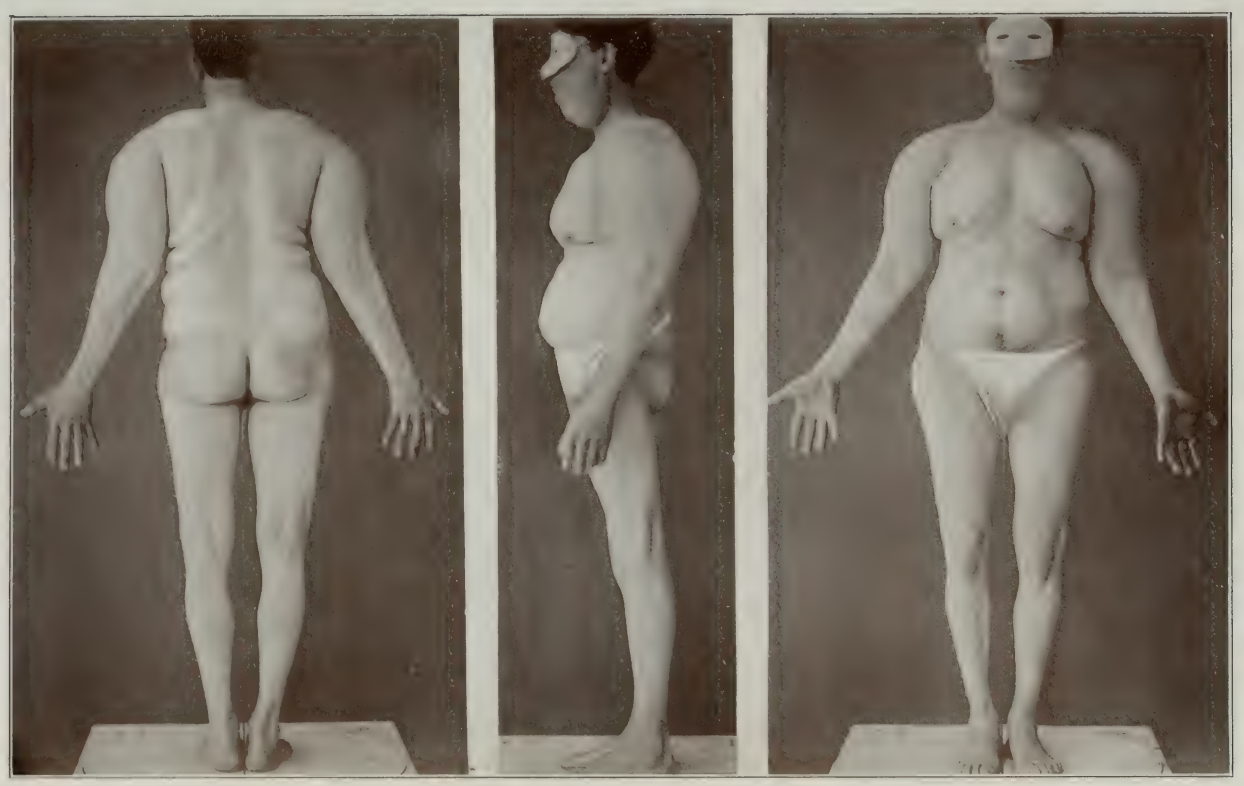
Multiple symmetrical lipomatosis. Hemiplegia.

in sweat secretion, cyanosis of the extremities, dermographia, trophic ulcers, and subcutaneous ecchymoses have been described.

Prognosis and Treatment.—The prognosis as to life is good, but as to cure is bad. In the majority of cases the disease is very refractory. Thyroid gland in ascending doses has been of benefit, in a small number of cases, in reducing the pain and the fat tumors. Aspirin and salicylates have been used with some benefit to relieve the pain and tenderness. Massage, baths, diet, etc., have been of only temporary benefit. The tenderness over the nerve trunk has a tendency to disappear as the disease advances.

[1] *Journal of Nervous and Mental Disease*, October, 1900, xxvii, No. 10, p. 519.

PLATE XV



Adenolipomatosis. (Case of Dr. C. K. Mills.)

PART IV.

DISEASES OF THE MUSCLES.

CHAPTER XXIV.

MYOSITIS.

By WALTER R. STEINER, M.D.

Definition.—Inflammation of the muscles. The voluntary muscles are, generally, alone involved, although the heart muscle may become affected, especially in the variety known as polymyositis hemorrhagica.

Myositis has long been recognized as occurring independently or in connection with certain diseases. Its classification, however, presents considerable difficulty, for our knowledge of this subject is as yet in a somewhat chaotic state. Dujardin-Beaumetz and others have endeavored to divide myositis into the acute and chronic varieties, which would greatly simplify matters. But unfortunately, as Lorenz has pointed out, each variety is subdivided into acute, subacute, and chronic types, although the syphilitic and tuberculous forms have an especially chronic character. At present, Lorenz's division seems the most preferable, but we should remember, in using it, that this classification may be, after all, as Lepine suggests, only applicable for clinical convenience. Certainly the recently reported atypical cases of Baer, Bevill, Mery, Terrien and Génevrier, Murrell, Sick and Gottstein bear out this idea. It is possible that another decade may bring forth a more rational division, for Lorenz has recently reported a case of non-suppurative myositis in which a protozoön-like body was found in the excised muscle. Bacialli's, Georgievski's, and Bauer's findings of bacteria in their cases (to be subsequently referred to) are also of interest in this connection. The skin coccus, however, appears to have been the germ found in the first two cases, but the results of the microscopic examinations in Bauer's and Lorenz's patients suggest the possibility of placing all instances of the suppurative and non-suppurative myositides into one large group—the infectious myositides—as Kader[1] proposed in his monograph on *Myositis*, some eight years ago.

We shall limit ourselves to the consideration of the primary myositides. The examples of myositis found in pyæmia, ulcerative endocarditis, actino-

[1] *Mitth. a. d. Grenzgeb. d. Med. u. Chir.*, 1897, ii, 617.

mycosis, erysipelas, gonorrhœa, pneumonia, typhoid fever, and other infectious diseases result from secondary processes in these maladies, and are discussed under their appropriate headings. In tuberculosis, the so-called primary or hæmatogenous form is seen when the infection is carried to the muscles by the blood stream from a distant focus, and is not due to an extension from contiguous tissues. The secondary form is much the more frequent here, as Zeller,[1] after a careful search, could only collect thirteen typical cases of the former from the literature on this subject, and add two from his personal observations. Two years later, Kaiser[2] added six more to this number.

PRIMARY SUPPURATIVE MYOSITIS.

Definition.—A single or multiple muscle inflammation, mostly acute, of bacterial origin, presenting clinically the picture of an acute infectious disease and generally ending in suppuration.

The first definite case of this disease was described by Foucault,[3] in 1869, under the term subacute suppurative myositis. Some years passed before another example was observed by Nicaise.[4] In 1887, Suard,[5] in his thesis, collected 14 cases from the different published reports, while Brunon,[6] in his thesis in the same year, grouped 23 instances under this heading. Walther,[7] subsequently, found 19 cases, which he considered typical. In 1898 Lorenz carefully examined the above lists and reduced the number to 11. He also gathered together 7 more cases, and gave a detailed account of one of his own. Since then, Miyake,[8] Abram,[9] and others have increased the number, as well as the twenty-five Japanese investigators, whom Miyake names as having studied this disease in Japan, after Scriba's initial work there. In consequence of their labors, Miyake states that there are about 250 cases reported in Japan, but adds that some of them have been incorrectly diagnosed. Different names have been given to this malady besides the one mentioned. Nicaise used the designation diffuse suppurative myositis, while Hayem preferred the term infectious myositis, which Scriba also adopted. Walther used the words idiopathic, acute, suppurative muscle inflammation as more correctly denoting the character of the affection.

Etiology.—Suard was the first to conjecture that the real cause of this disease was of infectious origin, which Scriba[10] and Brunon later proved by finding microörganisms in the pus from the muscle abscesses. The results of the bacteriological labors of these observers were described by them in subsequent communications, but Scriba's work, appearing only in Japanese medical literature, has been pretty generally overlooked. The latter observed the *Staphylococcus pyogenes aureus*, while the former found streptococci, staphylococci, and an undifferentiated bacillus, the streptococci predominating. Brunon consequently thought that the disease was not

[1] *Beitr. z. klin. Chir.*, 1903, xxxix, 633.
[2] *Arch. f. klin. Chir.*, 1907, lxxvii, 1033.
[3] *Bull. de la Soc. anat.*, 1869, 506.
[4] *Revue mens. de Méd. et de Chir.*, 1877, i, 51.
[5] *Contribution a l'Étude de la Myosite aiguë suppurée*, Bordeaux, 1877.
[6] *Contribution a l'Étude de la Myosite infectieuse primitive*, Paris, 1887.
[7] *Deut. Zeitschr. f. Chir.*, 1887, xxv, 260.
[8] *Mitth. a. d. Grenzgeb. d. Med. u. Chir.*, 1904, xiii, 153 (Bibliography).
[9] *British Medical Journal*, 1904, ii, 1341.
[10] See Miyake, *op. cit.*

due to a fixed variety of bacteria, but to any kind of pus-producing micro-organism. Other investigators, as Lorenz, Honsell, Kojima, and Araki,[1] and Ito and Sinnaka,[2] have sought for bacteria in their cases, and have found, in every instance, the *Staphylococcus pyogenes aureus*. Sato[3] twice obtained a mixed culture of staphylococci, streptococci, and an encapsulated diplococcus, resembling the pneumococcus; in another case, he cultivated staphylococci and streptococci. Miyake has recently reported his results from a study of 33 cases, observed in one and three-quarters years' experience in private practice, at Tokustuma and in the hospital at Osaka, Japan. Cultures were taken in all but one, in which the muscle inflammation ended in resolution without suppuration. In 2 of the remaining 32 the cultures were negative; in 27 a pure culture of the *Staphylococcus pyogenes aureus* was obtained; in 2 there was a mixed culture of the above organism with the albus; and in one the streptococcus was alone seen. By animal experimentation, Miyake showed that these organisms were all highly virulent, and produced by inoculation a disease similar to that observed in man. In his paper he discusses the interesting question as to why the affection is more frequent in Japan than elsewhere, and considers three possible factors: (1) The climate and telluric conditions; (2) the racial characteristics; and (3) the nourishment (mentioned also by Ito and Sinnaka). He believes that the second and third factors play the more important parts.

Various portals of entry for the bacteria may be seen, such as small infected wounds, furuncles, or acne pustules, but, as Miyake states, they cannot be considered as the original foci of infection unless the bacteria they contain are similar to those found in the muscle abscesses. Occasionally the mucous membranes, apparently, permit the infectious organisms to gain entrance into the body. From these different foci they are carried to the muscles by the blood stream, so the disease should be considered as a septicopyæmic infection, with the abscess formation limited to the muscles, and the only reported blood culture confirms this theory. As muscles are very resistant to inflammation, the presence of a *locus minoris resistentiæ* is assumed, and various predisposing factors have here been assigned. Lyot, Walther, and others offer many suggestions, but none of them appear convincing, save trauma, and overexertion and hyperæmia of the muscles. Lorenz would separate traumatic myositis from the idiopathic form we are considering, but in the latter a slight trauma may appear, so that it seems impossible to draw a sharp line of distinction between them. Miyake has shown by careful animal experimentation that the above-mentioned three factors are important predisposing causes. He proved that if a muscle or some muscles were overworked, some of their fibers might be torn apart and punctiform hemorrhages might occur, which would afford good culture media for the circulating bacteria. Brunon thought the muscles most used were more apt to be affected, and five in Miyake's series seem to bear out this idea.

Age.—Age appears to have no relation to its occurrence, although it was formerly thought that the disease was more frequent in children. In Miyake's series, 18 were under and 14 were over twenty-five years of age.

[1] See Miyake, *op. cit.*

[2] *Deut. Zeitschr. f. Chir.*, 1903, lxix, 302.

[3] See Miyake, *op. cit.*

Sex.—The sex bears no direct influence on this affection. It is seen more commonly in men, as in them the predisposing causes of trauma and overexertion are more frequently observed. In Miyake's series, 21 were men and 12 were women. In Ito and Sinnaka's list of 10 cases, 7 were men and 3 were women. It is more common in the laboring classes.

Season.—Some writers have thought the time of year, which has been variously given, had something to do with the onset of this malady. Fujiy,[1] however, claims it is most frequent when the laboring classes work in the fields and are subjected to the predisposing causes of cold and fatigue.

Pathology.—Three varieties of suppurative myositis have been recognized: (1) With large solitary abscesses in the muscles; (2) with disseminated abscesses in the muscles; and (3) with diffuse purulent infiltration in the muscles.

In primary suppurative myositis, most of the reported cases can be classed under the first heading. The skin and underlying connective tissue, placed over the affected muscle or muscles, are generally normal in appearance. The muscle itself is of a dark red to grayish red color, densely infiltrated with serum and very friable. The abscess, situated in the muscle, contains thick, greenish yellow pus, mixed with blood and tissue particles. Its walls are lined with gray or yellowish gray necrotic fibers. In the more severe cases, where the abscess has invaded the whole muscle, only a few shreds of muscle tissue may be seen hanging from the sarcolemma sheath (Chassaignac's case). Occasionally the muscle affected is described as pale, like the muscles of a fish, and exhibiting yellowish lines or streaks. It may also be bluish red in color, depending upon the degree and duration of the inflammation.

Microscopically the findings have varied somewhat. They are of a serous, seropurulent, and purulent character. Scriba declared that the interstitial tissue was not altered, but later observers have found it otherwise. Indeed, Sato went so far as to say that this myositis was properly of an interstitial variety, but Miyake states that his sections came from cases with metastatic muscle abscesses, and not from the cases of primary suppurative myositis. Miyake examined the muscle tissue in 14 of his own 33 cases and observed the interstitial tissue markedly increased in the purulent cases and infiltrated with mononuclear and polymorphonuclear cells. Occasionally this tissue had completely replaced the muscle fibers.

The different investigators agree in the main on the muscle changes, but not upon the extent of the same. For Miyake found most of the fibers in his cases unaltered, while Scriba described the majority of them he saw, in his personal observations, as swollen and showing a partial or entire loss of cross-striation. At times irregular cross-striations were noted. The sarcolemma sheath was much thickened and contained cells of varying sizes and shapes, while the perimysium was slightly infiltrated with small round cells. Hyaline, granular, and fatty degeneration was not noted by Miyake. Lorenz has described vacuolic degeneration. About the abscess walls there is a marked round-cell infiltration, and the muscle fibers are here almost completely destroyed. Farther out the fibers are readily seen, but they are shrivelled and without cross-striation. The muscle nuclei are generally somewhat increased. By the Gram stain, bacteria are found in clumps in

[1] See Miyake, *op. cit.*

the vicinity of the abscess wall, but are not seen in localities where the inflammatory process is less pronounced. Miyake believes the cases differ, so that now the muscle changes predominate, while in other instances the interstitial changes are most noticeable. In advanced cases there is an extensive amount of granulation tissue and a new formation of muscle fibers from the proliferated muscle nuclei.

Symptoms.—The onset is usually sudden, and most of those attacked have previously been in good health. A chill, followed by high fever, is generally the first symptom noted, but the patient may also complain of anorexia, general malaise, headache, profuse perspiration, and pains in the extremities. The pain is at first ill-defined, and resembles somewhat that seen in rheumatism. It soon becomes localized in the muscles, which are very painful. On examination, one finds here a tender, indurated swelling, which conforms to the shape of the muscle and is freely movable. Scriba describes the swelling as of a hard, board-like character. If it involves the long muscles, it is spindle-shaped in appearance, but if the broad muscles are attacked, it is hemispherical. The muscle itself is contracted, and active and passive movements are much limited on account of pain. The skin over the affected muscle is hot, but generally not reddened. There may be some œdema of the underlying tissues. At times an extensive erythema or ecchymosis is noted. The induration may be limited to only a portion of the muscle, or even its whole extent may be involved. Subsequently, within four to ten days, the swelling becomes softer and gives signs of evident fluctuation. In one case, however, this was delayed for thirty-one days. On incision, a muscle abscess is found and a thick, greenish yellow pus, slightly mixed with blood, is evacuated. If the incision is long delayed or neglected, the pus may penetrate the muscle sheath and infiltrate the surrounding tissues, leading to the formation of multiple abscesses in different parts of the body, and finally result in death (Scriba). Rarely the stage of induration ends in resolution.

One or many muscles may be attacked. If multiple, it appears in two forms: (1) The so-called typical form, which is multiple from the onset; (2) the atypical form, which begins as an isolated focus of infection and later becomes multiple (Miyake). In Miyake's series, one muscle only was involved in 18 cases, two in 12 cases, three in 2 cases, and five in 1 case. Tomada[1] has observed a case, however, in which eighteen muscles were affected, in fourteen of which suppuration occurred, yet the patient ultimately recovered. Walther, Sato, Fujiy, and Miyake find the muscles of the lower extremity are the most frequently implicated; those of the upper extremity being the next involved, but Brunon has observed the following in the order of frequency: Breast muscles, deltoid, triceps and biceps humeri, lumbar muscles, biceps femoris, and gastrocnemius.

Recurrences may take place. Two cases have been reported in which this happened after an interval of three and four months. The similarity between this disease and osteomyelitis, both clinically and bacteriologically, has been especially considered by Walther and Miyake. Brunon divides the cases into three types, viz.: (1) Malignant, resulting in death in a few days; (2) acute, in which recovery may ensue; and (3) subacute, a very light form. Some of his cases belong to other diseases, and a consideration

[1] See Miyake, *op. cit.*

of the typical instances of this affection thus far reported, leads us to place them under two headings, the acute and subacute.

Diagnosis.—If the disease is seen from its onset, this is generally relatively simple, provided the following two points be considered, which Scriba first called particular attention to, as being diagnostic of this affection: (1) The dense infiltration and swelling of the muscle; (2) the painful condition of the affected muscle, which is kept firmly contracted, and causes the extremity, or part of the body implicated, to assume various positions. If, for instance, the biceps brachii is attacked the arm will be flexed, or, if the rectus abdominis muscle be involved the body will be inclined forward. In each case the insertions of the muscles are more closely approximated, to lessen the pain which tension would increase. Occasionally osteomyelitis is simulated, especially in those cases in which the muscle sheaths of the implicated muscles have ruptured. In the latter, the disease rarely involves the surrounding tissues, but is seen extending to other parts of the body by metastatic foci. In doubtful cases, a wide surgical incision, combined with an inspection and palpation of the abscess cavity with the finger, will definitely differentiate the two conditions. Metastatic abscesses in pyæmia will at times need to be distinguished from this malady. In the former there is usually no dense infiltration of the concerned muscle or muscles, or, if present, it is extremely slight. The local disturbances are also absent or so trivial that the patient does not detect them.

Prognosis.—All uncomplicated cases have a favorable prognosis if seen early enough for the requisite surgical treatment. In Miyake's series of 33 cases there was only one death, and this was from a complication. After the pus is emptied from the muscle abscesses, the acute inflammatory symptoms subside very promptly, and complete healing takes place in the affected muscles, after an interval of from one and a half to three months. Rarely, the loss of muscle substance is replaced by scar tissue, which may cause severe contractures of the muscles. In cases in which early surgical treatment has been neglected, if the pus penetrates the muscle sheath and forms metastatic foci in other parts of the body, the prognosis becomes very grave. Muscle atrophy may follow the healing of the abscesses, but there is generally no subsequent functional disturbance.

The complications to be dreaded are pyæmia and pneumonia. Sato, Kurosawa, and Suzoki have reported cases in which a metastatic lung abscess was the cause of death. In Walther's case death ensued in the ninth week from an intercurrent endomyocarditis.

Treatment.—By the use of cold packs and other antiphlogistic means, the muscle induration may not undergo suppuration, and absorption may result. If fluctuation does occur, an early broad incision should be made and the pus thoroughly evacuated. It should be remembered that a previous negative exploratory puncture does not exclude the presence of pus, which may have been too thick to flow through the needle. Fujiy and Honsell firmly oppose surgical procedures unless pus is surely present, but in case of doubt it is better to err on the side of caution and open the indurated areas widely. If, after the myositis has subsided, contractures of the affected muscles ensue, massage and various orthopedic measures should be employed.

NON-SUPPURATIVE MYOSITIS.

Dermatomyositis.—**Definition.**—An acute, subacute, or chronic disease, of unknown origin, characterized generally by a gradual onset, with vague and indefinite prodromas, followed by œdema, dermatitis, and a multiple muscle inflammation.

The disease was unrecognized as a clinical entity until 1887, when E. Wagner,[1] of Leipsic, Unverricht,[2] of the Polyclinic at Jena, and Hepp,[3] of Kussmaul's clinic at Strasburg, almost simultaneously reported cases. Since then the number of cases published has rapidly multiplied. In 1893 Lewy reported three cases and collected twenty more in the literature, and two years later Köster added three more to this number. They were gathered, however, without any discrimination, and, under the careful scrutiny of R. Pfeiffer,[4] the number was reduced to eleven. The list in 1898 was increased to fifteen by Lorenz. During the following years different types have been again included in this group, so that now about fifty cases are placed here. In 1903 the writer, in a consideration of this disease, excluded the doubtful histories and found twenty-eight typical instances.[5] Three or four have since been reported.[6]

Etiology.—We are much in the dark as to the cause of the disease, although recent findings point more strongly to its infectious origin. Hepp and others have previously emphasized this view, and the presence of a splenic tumor, fever, and angina have seemed to support it. From Senator's time the following three theories have been advanced:

1. It is due to a specific microörganism (vegetable parasite). This view was gradually losing ground until recently, for bacteria have been frequently sought for in the inflammatory œdema and in the tissues, with negative results in every instance, save one (Bacialli's case), and cases of this disease, reported as being due to certain bacteria, have been shown to belong to another class of muscle inflammations. Bauer[7] and Georgievski[8] have reported cases of the allied affection, polymyositis hemorrhagica, which were probably due to staphylococci obtained in pure cultures from the tissues. In Bacialli's case the *Staphylococcus pyogenes albus* was also found, but his findings as well as Georgievski's can hardly be considered as conclusive in view of the universal presence of the *Staphylococcus pyogenes* albus in the deep layers of the skin (Thayer[9]).

2. It is due to an animal parasite. This idea was first advanced by Unverricht, who thought the parasite might belong to the gregarinæ. In

[1] *Deut. Archiv f. klin. Med.*, 1886–1887, xi, 241

[2] *Münch. med. Woch.*, 1887, xxxiv, 488.

[3] *Correspondenzbl. d. allg. Aerztl. Ver. v. Thüringen*, 1887, xvi, 203, and *Zeitschr. f. klin. Med.*, 1887, xii, 533.

[4] *Centralbl. f. allg. path. Anat.*, 1896, vii, 81.

[5] *Journal of Experimental Medicine*, 1903, vi, 407 (Bibliography).

[6] *Journal of the American Medical Association*, 1908, l, 177. In this article Burley reports three cases and considers the recently reported examples of this malady. All of the latter, however, with the possible exception of one (which was also tuberculous), appear to be atypical.

[7] *Deutsch. Archiv f. klin. Med.*, 1899, lxvi, 95.

[8] *Bolnitsch. Gaz. Botkina*, 1900, xii, 696.

[9] *Boston Medical and Surgical Journal*, 1902, cxlvii, 313.

support of this theory, L. Pfeiffer[1] states that the muscle findings in this disease are similar to those seen in the muscles of horses and dogs infected with gregarinæ, and he adds that Virchow has mentioned cutaneous eruptions in hogs that were similar to the changes in the skin occasionally found in dermatomyositis. The only instance in which these parasites were found in man, before Lorenz's case, was reported in 1891 by Klebs,[2] who observed them in a case of muscle atrophy, where they were at first taken for muscle nuclei. In 1904 Lorenz described and pictured a sporozoön-like body he found in some cross-sections from the muscles of the forearm, excised from a typical case of dematomyositis of five months' duration. Unfortunately the muscle was not examined in a fresh state. Negative results have attended the careful search for parasites in seven other cases, in two of which L. Pfeiffer also examined the sections. This unsuccessful quest Pfeiffer would explain as due to the fact that the methods of preserving the tissues and preparing the specimens militate against a ready recognition of the parasite. They may be present but be overlooked, or, as they can cause a muscle inflammation by their presence or their toxin, the muscles containing them may escape microscopic examination.

3. It is due to a toxin. This view was given prominence by Senator,[3] to whom it was suggested by his second case, which began with symptoms of gastro-intestinal irritation after the patient had eaten stale crabs. Kell's case[4] is also somewhat similar, the symptoms appearing a few hours after the ingestion of fish. No gastro-intestinal symptoms were here noted. In addition to these, Boeck's case has been put in this group, as the disease was observed after the energetic rubbing of copaiba balsam into the skin. Boeck, however, does not consider this to have any etiological significance.

Köster[5] suggests that the symptoms may be due to a primary implication of the vascular system. On this assumption, Lepine[6] has proposed the term angiomyositis. It is interesting to note, in this connection, that Rosenblatt[7] has described a case resembling dermatomyositis, which showed thrombus formation in the vessels, degenerative changes in the vessel walls, with fibrin and leukocytes in and about the vessel walls. Cold and fatigue are said to play a very minor part, although occasionally they seem to be exciting causes.

Distribution.—Cases have been reported in the United States and in a number of European countries.

Race.—The Anglo-Germanic has furnished most of the instances, followed by the Latin and Scandinavian races. The case which was recently reported by the writer is the only one yet observed in the negro.

Season.—The time of year seems to have no connection with the disease. In the writer's collected series 10 were attacked in the winter, 5 in the spring, 8 in the summer, and 5 in the autumn.

Sex.—The affection has been observed, according to this series, in 17 males and 11 females. Its distribution among the sexes is probably about equal.

[1] *Die Protozoön als Krankheitserreger*, Jena, 1891, 2 Aufl., 208.
[2] *Festschrift Rudolf Virchow zu seinem 71 Geburtstage*, Berlin, 1891, 31.
[3] *Deut. med. Woch.*, 1893, xix, 933.
[4] *Journal of the American Medical Association*, 1896, xxvi, 967.
[5] *Deut. Zeitschr. f. Nervenh.*, 1898, xii, 150.
[6] *Revue de Méd.*, 1901, xxi, 426. [7] *Zeitschr. f. klin. Med.*, 1897, xxiii, 547.

Pathology.—Of the 17 fatal cases in this series, autopsies have been performed in all but 7, and in 4 of these the excision of a piece of muscle was allowed. We have, consequently, a fair amount of data on which to base our conclusions as to the changes. With the exception of an enlarged and soft spleen, the pathological findings are limited to the muscles. Any or all may be attacked. It was early stated that the muscles of the eye, tongue, heart, and diaphragm were exempt, but later investigation has shown the eye muscles were implicated once (Strümpell's case); the tongue three times (Jacoby's, Strümpell's, and Köster's cases); the heart apparently three times (Kell's, and one of Lorenz's and Oppenheim's cases, although no microscopic examination was made in Oppenheim's case), and the diaphragm five times (Strümpell's, Köster's, Senator's second case, Wagner's second case, and Janowsky's and Wyscokowicz's case). Batten[1] states that the masseters usually escape. They were implicated in Boeck's, Strümpell's, and Unverricht's second case. Recently Lorenz[2] declares the implication of the heart has a deeper significance than was at first imagined. The cases presenting this complication show a special tendency to relapses, although mild and abortive at first.

The skin covering the muscles is firm and hard and generally does not pit on pressure, although œdema is usually present, but may be slight. On section the subcutaneous tissues present a firm, tense œdema, and are, as a rule, infiltrated with a yellowish, serous fluid. Microscopically, the muscles exhibit extensive changes, as Unverricht has shown in an illustration of their gross appearance in his first case. The muscles are swollen, pale red or pale yellow in color, or may reveal, occasionally, yellowish gray or diffuse reddish streaks. Hepp considers the muscles to resemble those of a dog. They are often strongly infiltrated with serum and quite moist. In consistency they vary, being hard and firm, or soft and boggy. They may be quite friable, as in Hepp's case, in which the left rectus muscle was found ruptured at autopsy. They are without lustre and of a dull, opaque appearance. Hemorrhages may occasionally be seen in them. Microscopically the changes are those of a parenchymatous and interstitial inflammation, and may vary in extent, being either focal or diffuse. Again, the different muscle changes may be seen, occurring in one and the same fiber. These are frequently separated from one another by the existing œdema or by mononuclear and polymorphonuclear leukocytes. Small hemorrhages may also be seen between them. The fibers are found in all stages of degeneration; they may be normal in size, œdematous or atrophied, coarsely or finely granular, hyaline or waxy, occasionally fatty. The striæ are normal, indistinct or invisible. Longitudinal or cross-cleavage of the fibers has been found, and vacuoles have been described in four instances. In many cases there is an increase in the number of muscle nuclei. Typical interstitial foci of small round cells are found in the perivascular connective tissue and, to a lesser extent, between the muscles. In the subacute and chronic cases the increase in connective tissue may be marked in both the perimysium externum and internum, and solitary muscle fibers in the process of degeneration may be surrounded on all sides by connective tissue. In five cases the bloodvessels were somewhat dilated and filled with blood.

[1] *Allbutt's System of Medicine*, 1899, vii, 461.
[2] *Berl. klin. Woch.*, 1906, xliii, 727, and *Deut. med. Woch.*, 1906, xxxii, 777.

Wagner has described new muscle formation as taking place in some of the fibers that had undergone waxy degeneration, while Senator has noted an abnormally large number of muscle spindles, two or three being found in each section. In the case described by the writer a peculiar picture was found in sections from the gastrocnemius muscle, which was called a muscle anomaly. As seen in cross-section it consisted of a collection of muscle fibrillæ cut transversely and encircled by a band of fibrillæ, cut longitudinally. Instead of one collection of fibrillæ, three or more bundles were at times thus surrounded, while the outer band was enclosed by the sarcolemma sheath. It has been described in five other instances (Münzer[1]). Münzer thinks it has no pathological significance, as it has been found in apparently normal muscle, in various diseases. It may, however, be the result of pathological changes in the muscles. Besides the sections exhibiting the parenchymatous and interstitial evidences of muscle inflammation, a peculiar blebbing of the sarcolemma sheaths was seen, which Hoen[2] had previously described in the muscles of a uvula.

Senator, Pfeiffer, and Lorenz consider the acute interstitial changes to be primary in this disease, and the degenerative muscle findings to occur chiefly in the second stage. They base this view upon the reports of the different observers on the pathological processes here met with. Illustrations of the microscopic changes are given by Wagner (in his second case), Jacoby, Strümpell, and Senator. In seven of the autopsies, bronchopneumonia was found as a terminal infection.

Symptoms.—The disease generally attacks persons in the prime of life and in the best of health. Fuckel's case, however, was noted in a girl after an attack of measles, and both of Wagner's cases had pulmonary tuberculosis, the second patient having tuberculous ulcers of the intestines. Senator's second case was a diabetic. The onset is almost always gradual, but may be sudden, with the prodromal symptoms of malaise, weakness, anorexia, pains in the extremities, or headache. These symptoms may be of several days' to three weeks' duration, or even longer, as in one case. Occasionally they are absent.

Pain.—Vague pains are next complained of, as well as a stiffness or rigidity in the extremities and back. These pains quickly take on a more definite character, become more or less circumscribed, and are localized in the muscles. Different muscle groups are then successively attacked, and eventually the whole skeleton musculature may be implicated. Later in the disease the pains become more severe, and are not only spontaneous in origin, but also are caused by active and passive movements. They are described as drawing, tearing, or boring in nature. In the most severe cases the patients lie utterly helpless in bed, as if completely paralyzed. The muscles involved are generally very painful on palpation, although the œdema does not cause them to be well defined. Muscle contractures have been observed in a few cases.

Fever is soon noted. It is usually of moderate intensity and intermittent or remittent in type. It rarely exceeds 104°, but just before death may rise several degrees above this height.

Œdema.—This appears with the fever and may implicate the whole body and extremities, the latter presenting at times a most ungainly appearance.

[1] *Virchow's Archiv*, 1905, Band clxxix, 591.
[2] *Journal of Experimental Medicine*, 1898, iii, 549.

It is generally first seen on the face, especially above the eyelids, and may cause the countenance to assume an immobile aspect, likened by Oppenheim to alabaster. The swelling is, as a rule, always noted in the extremities, being apt to involve the proximal parts, *e. g.*, the shoulder, upper arm, elbow, thigh, or inguinal region. It is not a symmetrical œdema, as the flexor or extensor surfaces are generally alone involved. It also varies greatly in character, as at one time it may pit on pressure, while at another a dense, hard infiltration of the skin is observed, the latter being the more usual. After the skin inflammation is noticed, it becomes more intense, and may remain localized over the affected muscles or spread to surrounding parts. Usually its duration is limited to the acute stage of the disease. The wrist- and ankle-joints are generally spared.

Dermatitis.—This is an early symptom, and varies greatly in character, being in different cases an erythema, a pseudo-erysipelas, an urticaria, a roseola, an eczema, or an inflammation resembling erythema nodosum. It may spread continuously or remain limited to the parts where it was first observed. At times it occurs only later in the disease. Its location is apt to be over the diseased muscles. It may disappear without leaving a trace behind or a pigmentation may indicate its former presence. In two instances, a dermatitis of a different type followed the disappearance of the first eruption.

Profuse *perspiration* and an *enlarged spleen* usually accompany the other signs and symptoms.

Nervous System.—No disturbances of sensation are, as a rule, met with, and the nerves are not tender on palpation. Hepp, however, refers to peculiar cramp-like pains in the later stages of the disease, of variable duration, and Wagner, Lewy, Lorenz, and Leube have noted paræsthesia during the course of the malady, shown by the patient complaining of feelings of formication. This, with the cramp-like pains, was especially marked in the writer's case, in which the patient complained of a sensation as if something was crawling down from the elbows of each arm to the fingers; it was particularly noticeable at night. The knee-jerks and the electrical reactions are usually either normal or diminished. In the mild cases the knee-jerks may be slightly increased, and, in the most severe instances, they may be totally abolished. Oppenheim states that there is, generally, a quantitative decrease in the electrical excitability of the muscles, and Lewy got a partial reaction of degeneration in his case.

Stomatitis and *angina* are at times seen, either early or late in the disease. In Lewy's case and in four of Oppenheim's, ulceration of the mucous membrane was observed. On this account the latter investigator has coined the word dermatomucosomyositis, to more rightly name this disease.

The extension of the affection to the muscles of respiration and deglutition was formerly considered the rule, and Löwenfeld names this as one of the three cardinal symptoms. It well accounts for the number of fatal cases reported, due to suffocation or bronchopneumonia. The urine is usually normal, but may contain albumin, and hyaline and granular casts may be found in the urinary sediment. The course of the disease may be characterized by improvement and relapses in the subacute and chronic cases, in which atrophy of the muscles may be observed. The acute cases last from one or two weeks to two months; the subacute, two to eight months, and the chronic forms from a year and a half to two years (Martini, Lorenz).

Diagnosis.—As a rule, no difficulty will be experienced in typical cases. Diseases presenting somewhat similar symptoms are: (1) Trichinosis, (2) neuromyositis, (3) primary suppurative myositis, and (4) syphilitic myositis. In the first, the initial gastro-intestinal disturbances and the discovery of trichinæ in the stools and excised muscles; in the second, the chain of nervous phenomena and the absence of a dermatitis; in the third, the presence of a focus of infection with the bacteriological report on the muscle examination; and in the fourth, the history of the patient and the objective findings, will generally sufficiently differentiate the affection. It is also well to bear in mind that one of Oppenheim's cases turned out, four years later, to be a typical example of scleroderma, while another in his series was so diagnosed by the physician who first attended him.

Prognosis.—As all the muscles in the body may be implicated, including those of respiration and deglutition, death may result from suffocation or bronchopneumonia. The early cases of this disease were almost invariably fatal, but some of those reported later have resulted in recovery. Of the 28 cases collected by the writer, 17 terminated fatally, so the prognosis is always grave. The outcome was fatal for the two patients in both extremes of life.

Treatment.—This should be chiefly directed to the relief of pain and to the keeping up of the patient's nutrition. Various analgesics have been tried for the former object, and among them we may mention aspirin and the salicylates, but no particular drug has as yet been found to offer any especial advantage. In severe cases, morphine has sometimes been necessary, in order to quiet the pain. Oppenheim employs hot air, the use of hot drinks and aspirin, while every second day he endeavors to cause the patient to perspire profusely. At the onset, or later, he uses thermomassage, and subsequently massage, gymnastic exercises, and electrotherapy.

Polymyositis Hemorrhagica.—Definition.—An acute, subacute, or chronic disease, of unknown origin, strongly resembling dermatomyositis, but differing from it chiefly in the presence of a greater or less amount of interstitial hemorrhage between the muscles and the occurrence of circulatory symptoms, caused by the implication of the cardiac muscle. The first example of this variety of myositis was observed by Veron[1] in 1888. It was not placed in this group, however, until Lorenz gave this class of cases a separate clinical existence and collected five similar cases, one being a personal observation. In 1902 Thayer again gathered together the previously reported cases, which with his own increased the number to ten. Hnatek[2] recently has added another to this list.

Etiology.—This is quite obscure, but staphylococci were found in two instances. The second case (Georgievski's), as elsewhere stated, is not conclusive "in view of the universal presence of the *Staphylococcus albus* in the deeper layers of the skin." In two cases, cold and fatigue seemed to bear some relation to the onset of the disease; in another case, angina was the first symptom, and the disease was thought to be a general infection following it. In still another, there was some preceding inflammation of the tissues of the neck.

Pathology.—The findings vary from simple hemorrhages between unchanged muscle fibers to extensive muscle degenerations and new connective-

[1] *Archiv. de méd. et de pharm. mil.*, 1888, xi, 481.
[2] *Wien. med. Presse*, 1905, xlvi, 917.

tissue formation. Lorenz has divided the changes into the acute and chronic forms. The first is characterized by intramuscular hemorrhages, which cause destruction of the muscle fibers, as well as the many muscle degenerations described under dermatomyositis. The second form is distinguished by the presence of connective tissue containing blood pigment and markedly atrophic fibers. For a fuller discussion of the pathology of this disease, one is referred to the article on Dermatomyositis.

Symptoms.—These described under dermatomyositis may be well used here, although in polymyositis hemorrhagica the usual absence of prodromal symptoms, a more sudden onset, and the occurrence of less fever are seen. Pain is, generally, the first symptom noted; it is definitely located in a small circumscribed area in the muscles, where, later, a nodular tumor, tender on palpation, develops. The extremities are usually first attacked. The condition is accompanied by more or less œdema, which varies greatly in its characteristics, for it may be as extensive as in dermatomyositis, but frequently it is more circumscribed and of softer consistency. Different muscle groups are gradually attacked, and the whole skeleton musculature may be finally involved. The skin may show a hemorrhagic or a measly eruption. The former is revealed by the presence of violaceous and purpuric spots, which, when fading, leave behind a yellowish green discoloration. Pigmentation may eventually be noted. Prinzing's case[1] exhibited well-marked muscle atrophy. Circulatory symptoms have been described in every case save one, due to the implication of the cardiac muscle. They are cardiac palpitation, tachycardia, arhythmia, and, more rarely, murmurs; all of which account for the cardiac weakness and collapse so frequently observed. An enlarged spleen is an inconstant symptom as well as hemorrhage, apart from that into the muscles and skin. Bleeding from the intestines has been described, and attacks of epistaxis, hæmaturia, and profuse menstrual flow. Nephritis is a frequent complication. The disease is generally of several months' duration. Fenoglio's patient[2] lived on for a year and a half, finally dying of pulmonary tuberculosis.

Diagnosis.—The sudden onset, the moderate fever, the character of the skin eruption, the cardiac involvement, and the muscle findings will readily cause it to be distinguished from dermatomyositis or other seemingly similar affections.

Prognosis.—Four out of the ten cases collected by Thayer recovered, so that the prognosis is about as grave as in the closely allied affection, dermatomyositis.

Treatment.—For treatment, one is referred to the article on Dermatomyositis.

Neuromyositis.—This term has been applied in about ten instances to cases which present the signs and symptoms of a myositis associated with those of neuritis. There seems to be some uncertainty as to whether the disease exists *per se* or whether the co-existence of two diseases is here observed. It is usually seen in chronic alcoholics, and is then accompanied by ataxia. Senator[3] first called attention to it in 1888, and subsequently Lipliawsky[4] made it the subject of his thesis.

[1] *Münch. med. Woch.*, 1890, xxxvii, 846.
[2] *Rivista clin. Arch. ital. di klin. med.*, 1890, p. 497.
[3] *Deut. med. Woch.*, 1888, xiv, 449.
[4] *Neuromyositis et Ataxia Alcoholica*, Berlin, 1901 (Bibliography).

MYOSITIS WITH SPECIAL TERMINAL LESIONS.

Primary Myositis Fibrosa.—**Definition.**—A single or multiple inflammation of the muscles, mostly subacute or chronic, which generally begins in the lower extremities, and presents but slight constitutional symptoms. Eventually the muscle tissue concerned is largely or wholly replaced by connective tissue, and quite pronounced muscle atrophy may be then observed.

The first case was reported by Gies,[1] in 1878, under the term myositis chronica, and since then about 12 additional instances have been observed. More recently Batten[2] has given it careful consideration, and in his paper details the full history of a patient, with the autopsy findings.

Etiology.—There has been considerable discussion whether this disease in its primary form is a definite entity. Some have claimed that it is only seen secondary to infectious or rheumatic conditions, but there seem to be good grounds for considering its independent existence as established. Kader regards the malady as an attenuated chronic form of the same process, which, in its acute stage, causes myositis serosa and purulenta (*i. e.*, primary, non-suppurative myositis). Hachenbruch[3] refers to it as being analogous to the sclerotic forms of osteomyelitis, while König[4] advances the view that it is a constitutional anomaly, by reason of which a tendency to the formation of connective tissue is seen. This last theory, according to Lorenz, would explain the finding of new connective tissue in quite freshly diseased muscles, and would account for the lack of sufficient etiological causes. Cultures from the tissues and search for microörganisms in the sections therefrom have been uniformly negative in their results.

Pathology.—The changes in the muscles are seen in two forms. In the first the implicated muscles are swollen and present to view a tumor-like mass. On palpation they are firm and hard. The skin and underlying tissues may be also involved, and then a dense œdema appears which does not pit on pressure. A brown pigmentation of the skin has been at times observed. In the other form, the muscle is changed into a dense, tendinous band. On section the affected muscles grate under the knife and reveal a hard, white surface in the most involved areas, but in the less affected portions show reddish yellow spots, which represent the remains of some of the muscle fibers. Microscopically there is a great increase in the interstitial tissue, which, in places, entirely replaces the muscle fibers. In other portions the fibers are atrophied and show a granular or fatty degeneration. Their cross-striations have disappeared, but their longitudinal striations are more evident. A relative increase of tendinous tissue is at times seen.

Symptoms.—The onset is usually slow and with slight symptoms. Indeed, the disease may take from several months to ten years to develop. Sharp pain is first complained of in the affected muscles, those of the lower extremity being usually the first implicated. Only one muscle or a single group of muscles are generally first attacked, although the beginning of the malady may be in several muscles. The pain in the concerned muscles soon forces the patient to go to bed, and, subsequently, a rigidity of the

[1] *Deut. Zeitschr. f. Chir.*, 1879, xi, 161.

[2] *Trans. Clin. Soc. Lond.*, 1903–1904, xxxvii, 12. He gives an excellent description of the disease, with references to the reported cases.

[3] *Beitr. z. klin. Chir.*, 1893, x, 73. [4] *Lehrbuch d. allg. Chir.*, 1889, p. 576.

affected limbs results and contractures ensue, the flexor muscles being especially prone to involvement. There is no fever, and the pain usually present is only of slight duration. The general condition of the patient is but little altered. Finally the affection may implicate most of the voluntary muscles of the body. The electrical excitability of the muscles is reduced, or may, in extreme cases, be wholly wanting. Disturbances of sensation have only rarely been reported.

Diagnosis.—Cases of this nature are very difficult to differentiate from other closely allied affections, for some tumors, as osteosarcomas, some forms of osteomyelitis, and a number of the varieties of non-suppurative myositis, simulate the malady very closely. Lorenz has well said a positive diagnosis is impossible without a histological examination. The slight or total absence of pain, when the affected muscle is palpated, is said to be characteristic of myositis fibrosa, as well as the gradual hardening of the muscle implicated and the cessation of the spontaneous pains, which are first well felt by the patients.

Prognosis.—The duration of the disease is long, but eventually a decided improvement is usually noted. However, it is ever well to remember that the affection may remain stationary.

Treatment.—Drugs are of no service, but massage and electricity are of benefit in ameliorating the symptoms and hastening the subsidence of the disease. By their use recovery has been noted in the cases of Gies, Kreiss, and Janicke.

Progressive Myositis Ossificans.—**Definition.**—A progressive inflammatory affection of the locomotor system, of unknown origin, characterized by the gradual formation of bony masses in the fascia, muscles, aponeuroses, tendons, ligaments, and bones, with resulting ankylosis of most of the articulations.

The disease was first described by Freke[1] in 1740, but it attracted little notice until Münchmeyer's paper[2] appeared in 1869, in which he carefully reported a case and made the malady a definite morbid entity, adopting for it, at De Dusch's suggestion, the designation progressive myositis ossificans. He also collected 12 cases from the literature. Since then other writers have made constant additions to this list. Gerber found 19 cases in 1875, Pinter 22 in 1884, Maunz 33 in 1892, Pincus in 1896 and Boks in 1897 found 38, in 1898 Roth 40, Matthes 42, Weill and Nissim, and Lorenz 51; De Witt[3] 78 in 1900. Most of these investigators have carefully excluded atypical cases. There are at present about 100 reported instances of this malady, and each one has generally been regarded as a clinical curiosity. Some of the patients have earned their livelihood by exhibiting themselves in museums, medical schools and hospitals.

Etiology.—In spite of the careful study devoted to this disease, its cause is as yet unknown. It is frequently described as of congenital origin, in the sense that it depends on some aberration of growth, congenitally acquired. This aberration of growth, some claim, comes from an ossifying predisposition or diathesis, and persons possessing it may contract the affection from some exciting cause, such as cold, unsanitary surroundings, trauma (either slight or severe), or single or many successive injuries. It may occur from

[1] *Philosophical Transactions*, 1741, 810.
[2] *Zeitschr. f. Med.*, 1869, xxxiv, 9.
[3] *American Journal of the Medical Sciences*, 1900, cxx, 295 (Bibliography).

no known factor. Mays,[1] Ziegler, and other investigators, who think that the bone formation is analogous to a new-growth, favor this view of ossifying predisposition or diathesis, first enunciated by Virchow to explain the origin of multiple exostoses. Nicholadoni,[2] Eichorst,[3] Kleen,[4] and others assert that it is a trophoneurosis and the changes are similar to those seen in progressive muscular atrophy and hypertrophy. The process here, however, is more extensive, and ossification finally results. Stonham[5] considered the disease a rheumatic condition, allied to muscular rheumatism and rheumatoid arthritis, while Brennsohn[6] and others declare it to be a reversion to a lower type, due to atavistic influences, a view which has little ground for support. There are, at present, two main theories. The first one considers the process of bone formation to be of an inflammatory nature, while the second view regards the bony growth as representing a tumor formation. Virchow and others, unable to decide this question, thought the process was on the borderland between an inflammation and a new-growth. The present trend of opinion appears to be toward the second view, which has much clinically to support it. Rolleston,[7] however, adheres to the former theory, and thus tersely expresses his opinion: "Myositis ossificans depends on (*a*) congenital weakness or want of resistance, and (*b*) a tendency to aberrant growth on the part of the mesoblast; as a result of diminished resistance the muscles are more susceptible to inflammation, while the tendency to aberrant growth subsequently shows itself in the calcification and ossification of the inflammatory products." Michelsohn[8] considers this affection to represent a blood anomaly, due to chemical or bacteriological irritants.

Age.—The disease is generally first noted in young persons, as Lorenz's records well show, for out of 45 cases in which the age at onset is given, 38 were affected before the fifteenth year; 11 of these showed the disease during the first year of life, 16 between the first and fifth years, and 11 between the ages of five and fifteen. Occasionally the patient does not fall a victim to the malady until later in life. Roger's patient was thirty-five years old when stricken. It appears, from the recorded cases, to begin earlier in women than in men.

Sex.—Males are more frequently attacked than females. Gerber gives the ratio as 4 to 1, while Rolleston says it is 5 to 1. In Weill and Nissim's series of 50 cases, 38 were men and 12 were women. To account for this, Pincus lays particular stress on obstetrical traumatism, and says the more frequent injuries of boys at birth, due to their better development, explains the preponderance of the male cases.

Race.—The Anglo-Germanic race has furnished most of the instances. According to Weill and Nissim's series, 20 cases came from Germany and 19 from England. The Latin and Scandinavian races contribute a few instances, as Russian, Swedish, and French cases have been reported.

Pathology.—In 1844 the first microscopic examination was made by Hawkins[9] of tissue excised from an implicated muscle, and in 1857 the second

[1] *Virchow's Archiv*, 1878, lxxiv, 147.
[2] *Wiener med. Blätter*, 1878, i, 476, 503, 529, 576.
[3] *Virchow's Archiv*, 1895, cxxxix, 193.
[4] *Deut. Zeitschr. f. Chir.*, 1894, xxxix, 301.
[5] *Lancet*, 1892, ii, 1485.
[6] *Berl. klin. Woch.*, 1892, xxix, 1163.
[7] *Clinical Lectures*, Philadelphia, 1904, p. 131.
[8] *Zeitschr. f. orthop. Chir.*, 1903, xii, 424.
[9] *London Medical Gazette*, 1844, xxxiv, 273.

case microscopically examined was investigated by Minkewitsch.[1] The disease, however, was confounded with other affections, and it was not until 1869 that Münchmeyer's classic article appeared, in which he accurately described the process of bone formation in the muscles. He recognized three periods or stages which have since been closely followed by other writers: (1) Stage of embryonic infiltration; (2) stage of connective-tissue induration; and (3) stage of ossification.

In the first stage the skin and subcutaneous tissue may appear normal, but the underlying affected muscle is much swollen and œdematous. Microscopically an extensive infiltration of the intramuscular and intermuscular connective tissue is seen. This infiltration consists in the formation and proliferation of an embryonic connective tissue, and is especially marked about the bloodvessels. In the second stage the embryonic connective tissue becomes organized and forms adult connective tissue, which, at first, proliferates more and more, but finally retracts and becomes a hard, fibrous swelling. On section it has the appearance of a fibroma, presenting a hard, white mass, in which the remaining muscle fibers resemble red striations. These fibers are more numerous at the periphery of the tumor where, microscopically, many of them appear normal. On passing inward toward the centre of the hard, white mass, the fibers, when present, seem atrophied or swollen, and frequently their cross-striations are lost. Fatty, waxy, and granular degenerations of the fibers have also been described, and many of them are completely destroyed. Their sarcolemma nuclei may be markedly increased and some may resemble giant cells. The increased intermuscular connective tissue is very rich in cells from the fusiform up to the large polymorphous type, which contains numerous karyokinetic figures. Other cells are also seen which resemble cartilage cells, without capsules, and later produce hyaline cartilage. Toward the middle of these fibrous swellings, small angular spaces are observed, in which formative cells lie, which later represent osteoblasts and bone corpuscles. The spaces are the osteoid trabeculæ. When these become calcified, the parts enclosed by the trabeculæ become bone marrow, and true compact and spongy bone is formed, when ossification, seen in the third stage, ensues. New bone is also formed in the fasciæ, ligaments, tendons, and preëxisting bones, in a manner similar to that just outlined. It is always of the fibrous, cartilaginous, or periosteal type, and histologically and chemically resembles true bone. By the fusion of several bony foci a larger mass is produced, and eventually a bony tumor, situated originally in a muscle, may extend beyond the confines of the affected muscle and give no indication of its point of origin.

Friedberg, who studied Wilkinson's case carefully, and Salmann[2] are the only two investigators who are opposed to this sequence of histological changes. They regard the disease as a primary parenchymatous muscle inflammation, with a secondary participation of the intramuscular and intermuscular connective tissue. It is proper to state that but one muscle was affected in the latter's case, and the sections therefrom were differently interpreted by Lexer when he had the opportunity to examine them, for he considered the connective tissue changes to be primary.

[1] *Virchow's Archiv*, 1867, xli, 412

[2] *Ueber die Myositis ossificans progressiva*, Berlin, 1893.

Symptoms.—The disease may exist for years before it is recognized. Many cases, indeed, have been diagnosed as "rheumatism," and their true nature only revealed at the period of bone formation. At times the onset may be so insidious that inflammatory appearances in the affected muscle, as well as pain, may be completely lacking. In typical cases the signs of a myositis are present; without any known exciting cause or after trauma, which may be very insignificant, a swelling is found in the muscle involved. The swelling presents a firm, doughy consistency. Pain may be present, confined to the muscle attacked or radiating in character. There is œdema of the overlying tissues, with some redness of the skin. The temperature is usually slightly elevated. In the course of a few days, or longer, depending upon the intensity of the process and the extent of the lesion, these symptoms vanish, but the muscle does not return to its normal state. It remains indurated, and finally a hard, tumor-like mass results. The disease may then become quite stationary for a variable period of time. Eventually, many of these masses form bony deposits, but some may remain as fibrous tumors, while others disappear, causing the muscles to undergo fibrous degeneration. In such muscles, Münchmeyer and others have described the occasional presence of fibrillary contractions. More rarely, the muscle may be entirely restored to its former state by the disappearance of the tumor. The process of bone formation occupies no fixed time, generally it is from two to eight months (the latter duration being seen in Koht's case). The bony change may be observed in the whole muscle or only in its fleshy portions, or, exceptionally, the tendons alone may be concerned. According to Münchmeyer, those muscles are spared whose two extremities are not inserted in the skeleton, but subsequent investigations have not borne out this statement. The changes resulting in bone formation are usually painless, although, occasionally, spontaneous pains are complained of, especially at night.

The muscles of the back and neck are generally the first involved. They were the first implicated in 21 out of 38 cases, while the muscles of the upper and lower extremities and of the face were the first attacked in the other instances (Lorenz). The ossification of the cervical ligaments and the muscles of the neck causes the head to be bent forward and the neck to be fixed. In extreme cases the flexion is so marked that the chin touches the sternum. The ossification of the ligaments, fasciæ, and muscles of the back varies very greatly. The bony deposits, if involving only a muscle, may conform to its shape and feel, on palpation, like freely movable, irregular plates. Very often the ossification has extended farther and the muscles are firmly attached to the skeleton. Generally, bony foci may be recognized in many muscles of the back, with no regular arrangement, like the ramifications of coral (Copping) or a geographical map of a mountainous region (Brennsohn). Minkewitsch describes the bony tumors of the back as resembling a stag's antlers. The vertebral column eventually becomes fixed, by the formation of bridges of bone, and scoliosis may be observed. In Pinter's case, a left scoliosis was noted in the cervical region, a right scoliosis in the dorsal region, and a left scoliosis again in the lumbar region. The scoliosis was so marked in one case that the left lower rib touched the iliac crest. A kyphosis, either cervical or lumbar, is much more rarely seen. The scapulæ early become attached to each other and to the thorax, while occasionally they are connected with the ileum. The movements of both

arms consequently are much limited. If the pectorals and latissimus dorsi are also involved, the arms are rigidly fixed on the thorax, which in some cases is described as a bony coat of mail.

Subsequently, from trauma or no known cause, the disease progresses, more muscles become implicated, and the corresponding joints fixed. The above outlined train of symptoms then ensues, except that fever may not be present. The upper extremities are usually earlier attacked than the lower, and a cicatricial shortening precedes the ossification, so that the limbs are held in a contracted position. The arms are generally fixed at the shoulder and, by the ossification of the biceps and anterior brachial, flexed at the elbow. The fixation of the iliofemoral articulations, as well as the ossification of the gluteal muscles, cause the hips also to be slightly flexed at the pelvis. This posture, with the forward projection of the head, displaces the patients' centre of gravity and gives them a precipitous gait, their knees being generally fixed in extension or slightly flexed. The forearms, hands, legs, and feet are only rarely involved. If the lower intercostal or abdominal muscles are implicated, the respiration may be upper costal in type.

Finally, the temporals, masseters, and pterygoids are attacked, and the patient is unable to move his lower jaw, which may be somewhat atrophied at this period. To overcome the difficulty in feeding thus induced, teeth and a portion of the alveolar process of the lower jaw have been removed. The mimicry facial muscles, the muscles of the eye, tongue, diaphragm, heart, perineum, genital apparatus, and sphincters are unaffected. The electrical excitability of the muscles varies. With the galvanic, the anodal closing contraction appeared before the kathodal closing contraction in two cases. The response to the faradic has generally been described as normal or decreased. Pinter got a reaction of degeneration.

In women who contract the disease the menses generally cease, or, if they have not yet appeared, they are frequently long delayed.

In addition to all these symptoms, the presence of exostoses has been frequently described. They are usually seen on the internal surface of the arm, the anterior aspect of the tibia, the upper part of the fibula, the ribs, or where the long bones approach the skin. The frontal bones and the phalanges of the fingers are also other sites where they have been observed. They may subsequently disappear. In about 75 per cent. of the cases reported a peculiar deformity of the great toes and thumbs has been noted, and occasionally the little fingers also have been involved. This was first described by Gerber, but Helferich[1] later directed more particular attention to it. The toes and thumbs are much shorter than normal, due to the dwarfing of the metatarsal and metacarpal bones, and subsequent ankylosis of the interphalangeal joints. This gave the impression, before the introduction of *x*-rays, that one phalanx was absent. The great toes are, generally, directed outward and frequently lie under the second toes, giving rise to the deformity of hallux valgus. The condition of the toes and thumbs is known as microdactylia. It is interesting to note that it was observed in the father of Sympson's patient, although he was not subject to this disease. In Michelsohn's patient the deformity was seen in the toes at birth, but on the thumbs it was not detected until the seventh year. Other malformations,

[1] *Aerztl. Intelligenzbl.*, 1879, xxvi, 485.

such as lack of some muscles, atrophy of the testicles and scrotum, have been noted in individual instances.

Diagnosis.—No difficulty should be experienced in recognizing this condition in advanced cases. The age of the patient, the first localizations of the bony deposits, the ever progressing character of the disease, and the presence of exostoses and microdactylia are important factors in establishing a diagnosis. Multiple exostoses may sometimes be mistaken for it, but the location of these tumors at the diaphyses and epiphyses of the extremities, the arrest of their development past the age of twenty, their bony character from the onset, and the fact that the muscles are never involved, except secondarily, should suffice for a proper differentiation. The joint involvements seen in locomotor ataxia should never be confused with this malady, although some muscles near the affected joints occasionally undergo extensive ossification. In the disease we are discussing the joints are never implicated. Again, spondylitis deformans and the muscle dystrophies bear some relation to progressive myositis ossificans, but their proper differentiation should present no difficulty.

Prognosis.—The disease is essentially of chronic character, and relapses alternate with pauses in its progress. At times there appears to be a cessation of the symptoms for six, ten, or even twenty-three years (as in Koht's case), but the malady is ever a progressive one, and the slightest cause may induce the formation of bony masses, such as the mere palpation of a muscle. In one patient a relapse occurred in April for five successive years without any known cause. Eventually the patients become practically helpless and bedridden. Bedsores and abscesses about the bony deposits may result, and death may ensue from pyæmia or some intercurrent infection, such as tuberculosis, to which the patients seem susceptible, or pneumonia. Suffocation may intervene, due to the limitation of the costal breathing and the onset of œdema of the glottis.

Treatment.—Medical treatment avails nothing, although various methods have been tried. Hawkins and Gibney have used phosphoric and lactic acids to make the bony deposits soluble, but both had no success. Hydrochloric acid has been also suggested for the same purpose. Mercury, potassium iodide, arsenic, and the salicylates have been employed, as well as medicated baths and local iodine treatment. Paget, Rolleston, and others have given thyroid extract to their patients, but without beneficial results, although Rolleston hoped "it would be useful, as the thyroid gland seems to have a special association with connective tissue, or with the mesoblast," and he considered this affection a mesoblastic aberration. Hawkins, Gibney, and others had recourse to surgical measures, and some of the bony tumors have been removed. The result, however, has been most unsatisfactory, as there has been a recurrence at the site of removal in almost every instance. Still, in necessary cases, as when the lower jaw is fixed, operative measures are justifiable. The most important point as regards the treatment of the disease is prophylaxis. By exercising precautions against trauma and cold, in the care of the patient, the affection can frequently be prevented from spreading. Occasionally, even these measures will not check the progress of this malady.

CHAPTER XXV.

THOMSEN'S DISEASE. MYOTONIA CONGENITA.

By WALTER R. STEINER, M.D.

THOMSEN'S DISEASE.

Definition.—An affection characterized by tonic muscular cramps at the beginning of voluntary movements.

The disease was named after a Danish physician, J. Thomsen, of Kappeln, in Silesia, who was a sufferer from it, and in whose family it had existed for five generations. Its subjective symptoms were well described by him in 1876, in a paper entitled, at Bartel's suggestion, to whom he submitted the manuscript, "Tonic Cramps in the Voluntary Muscles in Consequence of an Inherited Psychical Disposition."[1] Previously it had been observed, in all probability, by Charles Bell[2] in 1832; Benedikt[3] in 1864; and von Leyden[4] in 1866; but Bell's and Benedikt's accounts are so fragmentary that Guttman[5] rightly assigns the credit of the first accurate description of this malady to von Leyden. Many writers have subsequently made important contributions to our knowledge of this subject. Strümpel[6] first named it myotonia congenita; later, Weichmann[7] added the word intermittent to this designation, and Süsskand[8] the phrase "in eunte motu." Westphal[9] would prefer to call it after Thomsen. Since Erb[10] collected 28 cases in 1886, the number has rapidly multiplied, for three years later he found 46 reported instances,[11] and nine years subsequently Niedendarp noted 58. More recently (1904), Hans Koch[12] has increased the list to 102. Some of these patients have been many times reported, as Jensen, the shoemaker, whom eleven observers have investigated.

Etiology.—Heredity is an important factor, for the disease may be directly transferred from the patient to the offspring, or merely the disposition to the malady may be transmitted. It may also be seen in the collateral branches of the family, or occur in several members of the same family, without direct heredity. In 1890 Hershill[13] stated that there were fifteen

[1] *Arch. f. Psychiat.*, 1875, vi, 706.
[2] *The Nervous System of the Human Body*, third edition, 1836, 436.
[3] *Nerven Pathologie und Electrotherapie*, first edition, 1864, i, 136.
[4] *Klinik der Rückenmarks Krankheiten*, 1874, i, 128.
[5] *Deut. med. Woch.*, 1892, xviii, 261.
[6] *Berl. klin. Woch.*, 1881, xviii, 119.
[7] *Ueber Myotonia intermittens congenita*, Breslau, 1883.
[8] *Zeitschr. f. klin. Med.*, 1894, xxv, 91.
[9] *Berl. klin. Woch.*, 1883, xx, 153.
[10] *Die Thomsen'sche Krankheit*, Leipzic, 1886.
[11] *Archiv f. klin. Med.*, 1889, xlv, 524.
[12] *Ueber Thomsen'sche Krankheit*, Leipzic, 1904.
[13] *British Medical Journal*, 1890, i, 242 (Bibliography).

families reported in which the disease thus existed. Bernhardt thinks that the marriage of blood relations may be of some etiological moment, as two members of the same family (a brother and a sister), whose parents and grandparents were cousins, came to him with the disease.

Occasionally, without heredity or family taint, the disease comes on in childhood, and has been found associated with a fright, a fall, or a dog-bite. These factors are probably not the cause, however, and we may conceive of the malady as being overlooked, on account of the mildness of the symptoms, until the above-mentioned accidents first attracted particular attention to the child. Until then no physician may have been called. Apart from these, other cases exist in which the symptoms have not appeared until later in life. In some instances, as in Thomsen's family, there is a marked neurotic family history, but Hale White[1] does not consider this to have much bearing on the etiology of the affection, and adds that the patient himself is rarely of neurotic habit.

Age.—The disease generally comes under observation when the patients are about twenty years of age, but cases are not rare at puberty. If the symptoms develop in young children, they usually pass unnoted until puberty is reached. Then, for the first time, an awkwardness in different movements and an inability to take part in the games of their comrades is observed. Sometimes they find they cannot get up quickly from the school bench when called upon to recite, or a soldier's career may first reveal the condition by the clumsiness and awkwardness with which the different movements are executed. In fact, in some instances in which this malady has been undiagnosed, such a career has caused much suffering, as these movements have been explained as due to simulation and extreme clumsiness. Angell's case was that of a German soldier, who deserted from the army on account of the cruel punishments given for his marked awkwardness in executing the manual of arms. This patient's brother, also in the German army and likewise afflicted with Thomsen's disease, was frequently similarly punished, until, unable to stand the constant penalties and disgrace, he committed suicide.[2] It was Thomsen who first pointed out the importance of this disease from a military standpoint, his son having frequently endured much in his army experience. When a diagnosis has been made in infancy, as in Friis' case, a difficulty in sucking, an immobility of the countenance after weeping, an awkwardness in bodily movements, or a panting respiration may be observed.

Sex.—Males are much more frequently attacked than females. In Niedendarp's list of 58 cases, 52 were men, while only 6 were women. In Hans Koch's list of 102 instances, this inequality was likewise very apparent, as 91 were men, but only 11 women. Of the 91 men, 11 had been soldiers.

Race.—Cases have been reported in Germany, France, Italy, Russia, Sweden, England, and in the United States. It appears to be more common in Germany and Scandinavia than elsewhere.

Pathology.—The material for the study of this disease has come mostly from muscles excised during life, as but one autopsy has been performed. This autopsy was reported by Déjèrine and Sotta[3] in 1895. The patient succumbed to an attack of acute nephritis with uræmic symptoms. During

[1] *Allbutt's System of Medicine*, 1899, vi, 467.
[2] *Journal of Nervous and Mental Disease*, 1891, xviii, 807.
[3] *Rev. de Méd.*, 1895, xv, 241.

the year prior to his death he was attacked by a chronic, exfoliative dermatitis, but otherwise had been in good health. The central and peripheral nervous systems are said to have been normal, but the cerebrum and cerebellum were not microscopically examined. There was a marked serous infiltration of the entire body, hydrothorax, hydropericardium, and œdema of the lungs, besides the special muscle changes. In the earlier cases, before Erb's monograph was published, the examinations of the muscles were negative, although they were investigated in five instances. In 1886 Erb's work appeared, in which he detailed the complete histories of two patients, with protocols on the examinations of the portions of muscles taken from each of them. He also gave a report on some muscle sections which were from a man who had died soon after an operation for carcinoma of the intestines. These sections showed pictures so similar to those seen in his two patients that he investigated the man's past history, and found him to have been another example of Thomsen's disease.

In Erb's personal cases the marked hypertrophy of the muscles affected was very noticeable while the skin over them seemed normal. On palpation the muscles possessed a certain elasticity and appeared to be in a somewhat contracted state. Some of them even revealed a board-like hardness. When called into action they felt much firmer than a normal muscle would feel under the same circumstances. Their color on section offered nothing distinctive. Erb claimed he could distinguish with the naked eye the solitary muscle fibers. Microscopically, the stained specimens exhibited changes most marked in the muscle fibers, although the connective tissue was also somewhat implicated. The fibers, individually, showed considerable hypertrophy, some of them being twice and even four times the diameter of normal fibers. In fact, 70 to 75 per cent. of all the muscles measured from 60 to 140μ in comparison with the normal measurements of from 20 to 65μ. The largest fiber had a diameter of 195μ. On cross-section the bundles of fibrillæ did not retain their normal polygonal form, but were much rounder than usual, with blunt edges, some being even almost circular in shape. The appearance of the fibers was also more homogeneous than normal, as there was an evident loss of cross-striation. Longitudinal sections showed the fibers to lack their normal parallelism, for they were curved and bent in all directions, and provided with swollen, irregular borders. The cross-striations appeared finer and more delicate than usual, while occasionally they were wanting and pronounced longitudinal striations were noted, or the fibers presented a very homogeneous aspect. In one of his cases, vacuoles were present but they were not of very frequent occurrence. They were of varying sizes, sharply marked off from the muscle fiber containing them, and generally somewhat eccentrically placed. In shape, they were inclined to be ovoid. They contained a finely granular, homogeneous mass as their contents, or a mass appearing as a membrane or coagulum provided with smaller vacuoles. Apart from these abnormalities, the increase in the number of nuclei was even more striking. On cross-section they were apt to be located next the sarcolemma sheath, and averaged 6.5 nuclei to each fiber, in a calculation of 100 fibers, while a similar calculation for 100 normal fibers gave only 1.8 for one specimen and 1.67 for another. At times the nuclei were found in the centre of the fiber, singly or in clumps. They were not so regular or sharply outlined as normal, and seemed larger and plumper. In longitudinal sections they presented long rows of six to twelve to twenty

in number, and were generally arranged along the border of the fiber, in lines parallel to the fiber's direction. The connective tissue also showed a moderate increase, but was not to be likened to any inflammatory or degenerative connective-tissue growth.

This picture was subsequently confirmed by various observers, although certain variations and new peculiarities were noted by many of them. The muscle hypertrophy was seen by all, but no measurements of the enlarged fibers have exceeded those given by Erb for the widest he observed. The widest fiber noted by Martius and Hansemann measured 144μ, while Déjèrine and Sotta and Wersiloff report those of 180μ and 170μ, respectively. Déjèrine and Sotta thought the hypertrophy was of purely functional origin, while Schiefferdecker and Schultze[1] suggested that it increased with age. These last two investigators have estimated by more accurate measurements the breadths of the fibers, and give the following as their results: 1.25 per cent., 20 to 40μ; 13.75 per cent., 40 to 60μ; 34.25 per cent., 60 to 80μ; 39 per cent., 80 to 100μ; and 1.5 per cent., 100 to 120μ. In addition to the hypertrophy, Déjèrine and Sotta, Jacoby,[2] Joseph Koch,[3] and others describe pronounced degenerative changes in the muscles. In Déjèrine and Sotta's case, two kinds of muscle changes were noticed, the one affecting the specific tissue of the fiber and the other the indifferent protoplasm, causing the fibers to be more homogeneous and to show the Cohnheim fields more distinctly. In later stages there was a splitting of the fibers and a dissociation of the sarcous elements, which lay in a cloudy, amorphous heap in dilated sarcolemma sheaths. Finally, the resulting loss of muscle tissue was evinced by vacuoles and empty sarcolemma sheaths. A few examples of solitary atrophy of the muscle fibers were found, and some striated muscle masses were detected without their encircling sheaths. The nuclei were frequently very irregularly situated. Their case is also of interest, as the findings varied in the different muscles examined, being most markedly expressed in the diaphragm muscles and least so in the tongue. They claimed they could trace the progress of the disease in the muscles, and described the first stage as mainly affecting the nuclei, which were greatly increased, and were almost as numerous as they were in other implicated muscles of the body, although the fibers here were not markedly hypertrophied. All these variations from the normal fiber these authors consider not as the cause but rather as the result of the disease. They also regard the degree of alterations present as somewhat proportional to the severity of the symptoms.

In Jacoby's second paper, published nine years after the first, his views are considerably modified. The hypertrophy is there regarded as due to the abnormal contractility of the muscle after its excision. If this is prevented by proper fixing, immediately after excision, the sections, subsequently cut, approximate closely to normal. One of his muscle sections slipped from its fastenings and confirmed his theory by showing pictures similar to those previously noticed in Thomsen's disease. Consequently, he regards the alterations he saw as due to "serous infiltration of the connective tissue and to secondary changes in the parenchyma, thereby nutri-

[1] *Deut. Zeitschr. f. Nervenh.*, 1903, xxxv, 1.
[2] *Journal of Nervous and Mental Disease*, 1887, xiv, 129.
[3] *Virchow's Archiv*, 1901, clxiii, 380.

tionally produced."[1] This accords with Böttiger's criticism of Déjèrine and Sotta's interpretation of their muscle findings, for Böttiger claimed the œdema might entirely account for the muscle changes. Koch observed degenerative processes, associated with those of a regenerative nature. Into the interfibrillary spaces, where long rows of nuclei were situated, he noted an ingrowth of capillaries from the perimysium internum. Finally, a sheath would be formed to enclose a new fiber thus cut off. In this way two, three, or even four fibers could be formed from a single one. The degenerative changes resulted in the formation of vacuoles and empty sarcolemma sheaths, and, for the production of the latter, nuclear proliferation was an important factor. In the sarcolemma nuclei he found evidences of an active proliferative process by direct division. A marked increase in the number of nuclei has generally been noted, and some have detected hypertrophy of the individual nuclei, the increase in size being in breadth and not in length. A moderate increase in the connective tissue has not been as constantly found.

The work of Schiefferdecker and Schultze is of special interest, for, in addition to the muscle hypertrophy previously mentioned, they found granulations in the sarcoplasm, which they interpreted as an indication of a specific disease there. They also noted an increase in the number of nuclei, which sometimes appeared in very extensive rows, but no degenerative processes were described in any of the fibers or any increase in the fibers' number, such as Koch reported. The granulations were only noticed in those sections of muscle which had been hardened in a solution containing magnesium and sodium sulphate, with sodium chloride and 5 per cent. formalin (Jore's solution). They consisted of small granules, generally circular in shape, and dark black, dark brown, or blackish brown in color, with at times a very glistening appearance. The sarcoplasm was more or less markedly infiltrated with them, and consequently some fibers appeared quite dark on account of the many granules present, but others would reveal the existence of only one or two. They had no definite location, and the size of the fiber bore no relation to the number of granules present. Almost every fiber, however, contained some of them at one point in its course. They were not found in the connective tissue or in the muscle sections placed in other hardening agents. In the portions of the muscle kept for a longer time in alcohol the granules appeared smaller, and could now be seen infiltrating the tissue everywhere. Schultze thought the substance might be considered as the precipitate of a solution which had pretty thoroughly penetrated the muscle fibers. The nuclear changes to him seemed to be primary, and thus to confirm Déjèrine and Sotta's theory. They also seemed proportional to the muscle hypertrophy, which did not appear to be functional in origin. The fibrillæ also exhibited a peculiar change, a thickening, especially at their cross-striations, due possibly to some nutritional disturbance. It was first noted at the periphery of the fibrillæ, and travelled from there inward.

Concerning the *pathogenesis* of the disease much has been written, but it is nevertheless still wrapt in obscurity. (1) The psychopathic theory was first advanced by Thomsen, in view of the peculiar mental states, such as melancholia and hypochondria, frequently found associated. The theory

[1] *Journal of Nervous and Mental Disease*, 1898, xxv, 508.

found at first many adherents, but it has little clinically to support it, and is now pretty generally abandoned. (2) The neuropathic view attributes the disease to some disturbance of the central nervous system, possibly some functional change in the cord. Jacoby, at first in favor of the third theory, has returned to this view, and considers "the disease is due to an embryonal developmental disorder of the nerve cells, consisting in the more or less diminished resistance of these cells to the influence of certain toxic processes, and that these intoxications then are, in such predisposed individuals, the direct producers of the disease." Sieligmüller, Peters, Rieder, Westphal, Marie, and others have also formulated different theories, which can be grouped here. (3) The myopathic idea proclaims the muscles to be the primary cause of the malady. Erb mentions the second and third views, but does not positively commit himself in favor of either one to the exclusion of the other. Déjèrine and Sotta, however, incline strongly to this theory, and it has also a number of other supporters. Jolly[1] and Huet,[2] for instance, consider the myopathy of primary origin, for by repeated electrical stimulation the prolongation of the muscular contractions gradually disappear. This, they think, indicates some chemical change in the muscle substance. The former investigator also remarked on the similarity between the contraction curve in Thomsen's disease and veratrine poisoning.

Ringer and Sainsbury[3] have demonstrated a myotonic disturbance of the muscles in animals by the use of certain chemical substances, after the motor end plates have been paralyzed by curare. Koch[4] argues that the muscles showing such degenerative and regenerative processes, as seen in his case, are not as capable to do work as are the muscles wherein these changes are less pronouncedly expressed. Hence the symptoms observed in this affection. Bernhardt thought the muscles remained in an undeveloped condition, and refers to the contraction curve of the muscles of the newborn and of exhausted animals as similar. Schiefferdecker and Schultze regard the malady as due to a disease of the sarcoplasm, which consequently affects the fibrillæ, and that both are the cause of the clinically observed symptoms. The hypertrophy of the fibers and the nuclear increase are merely accompanying phenomena. The disease may be called forth in the muscles by an intoxication of their tissue, the theory thus fitting in with those of Jolly, Eulenburg, von Bechterew, Karpinsky, and Jensen, who consider this affection a disease of the metabolism. Jensen claims this is expressed by a hindrance in the process of assimilation and in the removal of the products of dissimilation.[5] These chemicophysical changes in the muscle may explain those of pathological origin, but what the former consists in, it is at present impossible to state. Geissler's theory,[6] that the disease is one of the motor end plates and of the muscle fiber, at the period of the development of the muscles, due to proliferative processes in the sarcolemma nuclei and to the participation of the nervous system, has practically no supporters.

Symptoms.—The characteristic symptom is the so-called myotonic disorder, which is revealed when voluntary movements of any sort are

[1] *Neurolog. Centralbl.*, 1890, ix, 438.
[2] *Nouv. Iconogr. de la Salp.*, 1892, v, 1, 92, 169, 229.
[3] *Lancet*, 1884, ii, 767, 816, 860.
[4] *Virchow's Archiv*, 1879, lxxv, 516.
[5] *Deut. Archiv f. klin. Med.*, 1903, lxxvii, 246.
[6] *Ibid.*, 1899, lxvi, 259.

attempted. This consists in tonic muscular cramps which forthwith ensue, inhibiting all movements for a short space of time and exhibiting a certain awkwardness and clumsiness of movement, which is very mortifying to the patient. Moreover, increased exertion to conquer this opposition leads only to renewed tonic, muscular contractions. After the same movements have been several times repeated, the muscles, with their antagonists, relax from their state of prolonged contraction, so that the awkwardness disappears, and subsequent similar movements can be executed normally. Occasionally the muscular rigidity is more marked during the second attempted movement. If, however, a few moments of rest intervene, or some sudden obstacle is seen, causing mental disquietude and bringing new muscles into play, the same awkwardness again appears. These tonic spasms or contractions of the muscles are never accompanied by pain, but are sometimes more marked if the patient be fatigued. Cold, heat, depression of mind, and hunger are also similar factors, which may not only bring on the spasms, but make them more severe. At times alcohol and warmth may cause them to lessen. Danillo thought the latter so acted when he gave his patient warm tea, and later proved it by then getting a normal myogram. The spasms may be seen not only in voluntary movements, but also in those of a reflex nature, as in coughing and sneezing, and after mechanical or electrical excitations. Passive movements are unaffected. Erb states the contractions are noteworthy for (1) their slowness, (2) their tonic character, and (3) their continuance after the cessation of the voluntary impulses.

The light cases may cause but slight inconvenience to the patients, who can easily conceal this muscular rigidity by cleverly executed movements. In the severe cases, the patients on attempting to walk appear as if chained to the floor, and the stiffness or rigidity which accompanies each forward movement of the leg must wear off before another step can be taken. With each successive step the stiffness is of shorter duration until it entirely disappears, and the patient may then walk without any further mishap. If, however, he should trip against a stone, turn suddenly around, or bring any muscle, not then in use, into play, rigidity of those muscles will follow, which may result in the patient's falling down. Similarly, in mounting stairs, the first ones seem to offer insurmountable difficulty, but when these are overcome, the rest are easily ascended; in handshaking, the grasp is slow and its relaxation is delayed, while the dynamometer shows the grasp is much below the normal standard; in eating, there may be an inability to close the mouth, when opened, until the spasm of the depressor muscle of the lower jaw relaxes and allows the masseters and internal pterygoids to act; in reading a book, the patient may be unable to raise his eyes for some minutes from the page, although earnestly desiring to do so, and in some cases strabismus is seen, due to spasm of the muscles of the eyeball. Similar difficulties are noted in speaking, dancing, drilling, or any movement requiring voluntary effort.

The muscles of the lower extremity are apt to be most frequently involved, although those in the upper extremity, as well as the tongue, masseter, eye, and diaphragm muscles, may be affected also. Occasionally the laryngeal muscles are concerned, in which case the speech is altered. Often the same patient shows an implication of the muscles of the extremities and the trunk, but the disease is not equally expressed in all of them, the chief difficulty being in the lower extremities. If the trunk muscles are attacked,

all forward movements, such as stooping, throw these muscles into a spasm, but they are unaffected in the movements required in parturition or defecation. Neither are the acts of swallowing, respiration, or micturition ever interfered with. More rarely, only a few groups of muscles exhibit this malady, as Oppenheim's patient, in whom the orbicularis palpebrarum alone suffered. The muscles are generally markedly hypertrophied to the naked eye and the patient appears to be of a very athletic build; his strength is below normal and not proportionate to his muscular development. In one of Erb's cases the myotonic disturbance seemed to be more pronounced in the more markedly developed muscles. Later observers have found an atrophy, associated with the hypertrophy, which, in some cases, appeared to be of the progressive muscular type. Hoffman[1] and Berg[2] have collected such cases from the literature, and the latter gives records of thirteen instances in which this atrophy appeared to him as a symptom of Thomsen's disease. His list includes three personal observations, in which sensory disturbances were exhibited.

Ballet and Marie, Pitres and Dallidet, Jensen, Hale White, and others have studied the muscular spasms in this affection by means of myographic tracings. They show that the muscular contractions and relaxations are considerably prolonged, especially the latter. In some instances the contraction has lasted for half a minute after the impulse of the will, which called it forth, had ceased to act. Some observers have found the latent period to be also prolonged, but Hale White, in his case, noted it to be of the same length as that of a healthy person.

The electrical reactions have been found as characteristic as the myotonic disorder, and have been collectively designated by Erb "the myotonic reaction." They are as follows: (1) The motor nerves show no increase of irritability to mechanical stimuli; (2) to the faradic current the motor nerves are quantitatively normal, but if the current be strong, the contraction produced on closing the current lasts much longer than it does in health; (3) to the galvanic current the motor nerves are quantitatively normal; but here, also, if the current be strong, the contraction lasts longer than in health; (4) mechanical stimuli applied to the muscles, as by hitting them, induce contractions more early than in health; (5) the faradic current applied directly to the muscles, if strong, sets up a contraction which lasts from five to thirty seconds; (6) when the galvanic current is applied directly to the muscle, K. C. C. and A. C. C. are equally easy to obtain; while in health, as is well known, K. C. C. is more readily elicited than A. C. C. In Thomsen's disease, even with weak currents, the contraction lasts longer than in health; with strong currents it lasts some seconds and relaxes very slowly. With the stabile application, well-formed, wave-like contractions are seen to proceed slowly from the cathode to the anode (Hale White). All of the reported cases have not shown an exact resemblance to Erb's cases, which gave the myotonic reaction as Hale White thus described it. They have in almost every instance, though, revealed a normal mechanical, faradic and galvanic excitability of the motor nerves, but an increased mechanical, faradic, and galvanic excitability of the muscles. The peculiar rhythmical, vermicular contractions have only been obtained in occasional cases by the

[1] *Deut. Zeitschr. f. Nervenh.*, 1900, xviii, 198.
[2] *Ueber Muskelatrophie bei Thomsen'sche Krankheit*, Bonn, 1904.

application of a strong and steady galvanic current. Erb, subsequently, did not attach much importance to them, but thought they could be obtained, in every case, by proper manipulations.

The tendon reflexes vary, being increased, normal, or absent. In two of Jacoby's patients the knee-jerks seemed at first exaggerated, but became weaker and weaker, after successive elicitations, until no response was obtainable. The knee-jerks later reappeared after a short interval of rest. There are generally no sensory disturbances, with the exception of rare paræsthesia. The quantitative urine examinations have yielded inconstant results.

Diagnosis.—The recognition of Thomsen's disease should, as a rule, present no difficulty, as the myotonic reaction and the myotonic disorder are observed in no other malady. Its general hereditary nature will also be of assistance in a diagnosis. Conditions are found, however, which present many forms of resemblance to Thomsen's disease and which may be confused with it. Talma, Fürstner, Jolly, and others have described instances showing an abnormal hyperexcitability to mechanical and electrical irritants. Although named myotonia acquisita, they have little in common with the disease we are now discussing, as Jacoby well states, and would be better termed intention spasm. He would apply the term myotonia acquisita to cases closely resembling Thomsen's disease, which come on after injury or overstrain. Another class of cases, presenting temporarily the myotonic disorder and myotonic reaction, he calls myotonia transitoria. Eulenberg's paramyotonia congenita is, also, a closely allied affection, and was noted in one family to the sixth generation. But here the myotonic reaction is absent and the muscular rigidity occurs only after the influence of cold. It is interesting to note that Delprat found two typical cases of Thomsen's disease, with temporary rigidity of the muscles, in consequence of the effect of cold, in a family with paramyotonia congenita, and also that Hlawaczek found the two diseases associated in one individual. Myotonia combined with progressive muscular atrophy or hypertrophy has been described, as above stated, by other writers, and Schultze, Bettmann, Mill and Kaiser, and others have noted its association with tetany and athetosis. Hoffmann, in one case, and Nalbandoff, in two cases (brothers), have found tabes as an accompanying affection. The former also observed a case with multiple neuritis as an additional complication. One of von Bechterew's patients was subject to attacks of gout. Pelz[1] has recently considered the atypical cases of Thomsen's disease, and places paramyotonia congenita in this category. He thinks, in the atypical forms, there are no absolutely pathognomonic symptoms, but considers the disturbances of the mechanical and electrical excitability as the most constant. If the disease develops late in life, he does not regard it as acquired, but as due to an exacerbation or a long latency of a disease which, although present, was slow in revealing itself.

Prognosis.—The intensity of the disease varies greatly; in the lightest cases the patients may hide the rigidity of their muscles by cleverly executed movements and experience no great inconvenience from their malady; the more severe cases unfit those afflicted from many occupations and cause them to undergo many hardships. In every instance it is an essentially chronic disease, which appears to progressively increase up to puberty or

[1] *Archiv f. Psychiat.*, 1907, xlii, 704.

even later. In some cases relapses and remissions mark the progress of the affection. It is never fatal by itself, and no recovery from it has ever been reported.

Treatment.—Nothing which has been hitherto tried in the way of treatment has been of any avail. Orchitic and thyroid extracts, atropine, strychnine, and a host of other drugs have proved futile. Hydrotherapy, gymnastic exercises, and massage have given favorable results in the hands of von Bechterew, Rosenbach, and Wersiloff, but nothing permanent has been accomplished. Thomsen thought he, personally, felt better the more active his life was. It appears that something may be done in the way of prophylaxis by cautioning the patient to lead a life as free as possible from mental excitement and injurious influences, such as cold.

MYOTONIA CONGENITA (OPPENHEIM).

Definition.—A general or localized flaccidity of the muscles in childhood, which is associated with a weakness or loss of the tendon reflexes. Attention was first called to this condition by Oppenheim in 1900. He has seen four or five marked cases and a few abortive forms. Spiller and Baudoin have reported the findings in their cases, which are the first to come to autopsy.

Etiology.—The disease is observed in children in the first months of life, and is essentially congenital in origin, without any hereditary tendency. Trauma at birth has not been noted in any instance. About eighteen cases have now been reported. In eleven of these, in which the sex was noted, five were boys and six were girls. Sorgente has published two instances of this affection in a brother and sister whose parents were first cousins. Rosenberg's patient was rachitic.

Pathology.—Oppenheim[1] considered the lesions were in the muscles, although he did not entirely exclude an affection of the anterior horn cells as the cause. Bernhardt[2] thought there was a defective development of the peripheral nervous system, or a degenerative inflammation of the peripheral nerves, from an unknown cause. Spiller[3] found the muscles from the sole of the left foot and the back of the trunk had a hyaloid appearance, the former showing a large amount of fatty connective tissue and a considerable increase of nuclei. The muscle fibers were small, especially those from the former situation and left calf. The transverse striations were well preserved, but the longitudinal striations were not so distinct. The nerve fibers within the sole of the foot were normal. There were no special changes observable in an examination of the brain, spinal cord, and peripheral nerves. Spiller consequently regarded the cause of the malady to be due to the arrested development of the muscle fibers. Allen J. Smith[4] subsequently studied the thymus gland from Spiller's case, and found a thickened capsule present with a marked interlobar, sclerotic change within the gland. There were also a considerable number of Hassall's corpuscles, of large size, present, with an endothelial proliferation in the thymus and Malpighian bodies of

[1] *Monatsschr. f. Psych. u. Neurol.*, 1900, viii, 232.
[2] *Neurol. Centralbl.*, 1907, xxvi, 2.
[3] *University of Pennsylvania Medical Bulletin*, 1905, xvii, 342.
[4] *Ibid.*, xviii, 206.

the spleen, arteriosclerosis in the thymus and spleen, lymph nodes in the lung, and a proliferation of the lymphoid elements of the mesenteric lymph nodes. From these findings Smith thinks some auto-intoxication may exist as the exciting cause. Baudoin[1] found an arrest of development in the anterior horn, without any inflammatory phenomena. The cells here were diminished in size and numerous axis cylinders had not yet been provided with myelin.

Symptoms.—The parents of the child so affected are usually the ones to note that the whole body of the child or only the limbs, especially the lower, are flaccid and motionless. This flaccidity may be so marked as to render the joints abnormally movable. Œdema is a trophic disorder, which may be present to a very marked degree. There is also a weakness or a loss of the tendon reflexes associated with this condition. Active movements may be impossible or only slightly impaired. The muscles innervated by the cranial nerves are never involved, and the cerebral function is undisturbed. The implicated muscles are flaccid, soft, and thin, but not atrophic. The muscles of the eye, tongue, throat, and diaphragm are not affected. The electrical reactions show a quantitative alteration or a complete absence, but in mild cases the reaction is normal. No disturbances of sensation are met with and the sensorium is clear.

Diagnosis.—The absence of family tendency as a factor will differentiate this affection from progressive muscular atrophy, while poliomyelitis occurs acutely in a previously healthy child. Amaurotic family idiocy shows a history of a family tendency, different microscopic and ophthalmoscopic findings, and an entirely different clinical history.

Prognosis.—The children attacked may show in time some improvement, but the outlook does not appear very encouraging. If the myotonia is generalized, the respiratory muscles are always attacked. In six instances bronchopneumonia caused the fatal termination.

Treatment.—There is no known special treatment. The use of massage, electricity, and nerve tonics is indicated.[2]

[1] *Semaine méd.*, 1907, xxvii, 241.

[2] For a further consideration of this interesting disease one is referred to the following articles: Rosenberg, *Zeitschr. f. Nervenh.*, 1906, xxxi, 130; Bernhardt, *op. cit.;* and Kundt. *Ueber Myatonia congenita*, Leipzic, 1906.

CHAPTER XXVI.

MYASTHENIA GRAVIS. PARAMYOCLONUS MULTIPLEX. PERIODIC PARALYSIS.

By DANIEL J. McCARTHY, M.D.

MYASTHENIA GRAVIS.

Synonyms.—Myasthenia gravis; pseudoparalytica; ascending bulbar paralysis; asthenic paralysis; pseudobulbar paralysis without an anatomical pathological basis.

Definition.—A disease with fatigue symptoms referable to the muscular system, due to an exhausted condition of nervous enervation, without definite pathology in the nervous system, and with minor changes (lymphocytic infiltration) in the muscles.

History.—Credit for the first lucid description of this disease must be given to Wilkes.[1] He described a case of bulbar paralysis in which no anatomical changes were found after death.

Erb, in the following year, reported a "peculiar and probable bulbar symptom complex," a syndrome composed of ptosis, paralysis of the jaw and neck muscles, weakness of the tongue, extremities, upper part of the face, and difficulty in swallowing. To Oppenheim, who in 1887 reported the next case with careful microscopic examination of the nervous system by more modern methods, and who later wrote a more extensive monograph of the subject, belongs the credit of establishing the disease as a clinical entity. Eisenlohr reported the next case in 1887. In 1890 two cases were reported by Bernhardt, one by Leonard Shaw, and an extensive and valuable description was given by Hoppe, from Oppenheim's laboratory, in 1892. Since that time extensive articles with collections of cases have been reported by Strümpell in 1896, and Campbell and Bramwell in 1891. Oppenheim, in his first case, considered the disease a neurosis of a chronic, progressive, and fatal type, manifested mainly by symptoms of glossopharyngolabial paralysis without atrophy. Later observations, especially those of Goldflam, showed that the affection was not necessarily fatal, and could go on to complete recovery, or run a course of many years with marked remissions. Goldflam also called attention to the fact that the affection might begin with an ophthalmoplegia, and that in some cases this was the only symptom. Weigert, in 1903, called attention to a persistent thymus, with lymphocytic infiltration in the muscles.

Etiology.—In the preparation of this article 180 cases were extracted, and two unrecorded cases have been added from the author's case histories.

[1] *Guy's Hospital Reports*, 1877.

Sex.—There were 83 males and 96 females. The preponderance of the latter can be accounted for by the influence of pregnancy, the menopause, and the puerperal state. This matter will be considered more fully later.

Age.—The incidence of the disease is most frequent in the third decade.

Age.	Males.	Females.
Under 10	2	2
10 to 20	8	18
20 to 30	21	42
30 to 40	18	20
40 to 50	24	5
Over 50	9	3

The average age at which women are affected is decidedly below that for men. As will be seen, males are more frequently affected during the fifth decade, women during the third.

Occupation.—The station in life and occupation have no decided influence on the disease.

Infectious Diseases.—Acute inflammatory processes occur with sufficient frequency immediately before the disease as to constitute, if not an important etiological, at least an important determining factor. If we consider all the possible sources of infection, including the nasopharyngeal infections, we find in our tables 39 cases. Influenza was present ten times, and among the other infections, scarlet fever, typhoid fever, diphtheria, syphilis, herpes, puerperal and postpuerperal pyogenic infections were noted.

Nervous Diseases.—The consideration of this disease by neurologists as a nervous disease has led to a very careful study of possible nervous influences. A distinctly neurotic history, however, is present in only a relatively small number of cases. The history of nervous disease in some member of the family was present in 35 cases. In most of these the types of nervous disease in parents or other members of the family were of such a nature that they could easily be excluded as having a distinct bearing upon the development of the disease. In 12 of these cases, for example, it was stated that there was a family history of "nervousness" without having any distinct statement as to the meaning of this term. The mother of one patient suffered with unilateral ptosis, the mother of another showed a defect of the ocular muscles, and migraine was present in still another case. Oppenheim has paid particular attention to evidence of a defectively constituted nervous system. Syphilis and alcoholism may be considered as negligible factors, the former occurring in 2 cases, the latter in 1. Pregnancy and puerperal conditions were present in 11 cases. In 2 of the writer's cases a miscarriage was regarded as the causative factor. In most of the recorded cases pregnancy has caused a distinctly deleterious influence on the course of the disease. In one recorded case, however, the patient felt very much improved during the pregnant state, but she was much worse during lactation. The menstrual period has a similar effect; patients are decidedly worse at this time.

Pathology.—The pathological changes are mainly confined to the muscles. The nervous system in the vast majority of cases is entirely normal. Weigert, in a case of myasthenia gravis, which presented lymphosarcoma of the thymus gland, found at autopsy an accumulation of small round cells in the endomysium and perimysium, and considered them as metastasis from the

thymus tumor. In subsequent reports these accumulations of cells have been termed lymphorrhages, and inasmuch as they may occur without primary malignant disease, are looked upon as lymphoid structures. They may be present when the thymus rest is normal. Examination of a muscle of an affected case will show the muscle fibers to be perfectly normal. Within the area of lymphoid infiltration, however, a few fibers may be atrophied and lack striation. A lymphorrhage or lymphoid infiltration occurs as microscopic accumulations of an irregular shape between the muscular fibers, and only rarely infiltrating them. They consist for the most part of small lymphoid cells from one to one and a half times the diameter of a red blood cell. This smaller type of cell resembles the cells of the thymus, but is usually larger than the small cells of the fetal thymus. A few cells of a larger type, containing a relatively larger amount of protoplasm and a small nucleus, are occasionally seen. Polymorphonuclear leukocytes are only exceptionally present. A loose reticulum is present between the cells. The composite structure closely resembles adenoid tissue, and the term "lymphorrhage" is an appropriate one. Capillary hemorrhages are not infrequently seen in the neighborhood of the lymphoid accumulation.

When these changes occur they are constant in affected muscles. Of the 29 autopsies reported since they were first described, there is a record of examination of the muscles in 16 cases, and lymphorrhages were present in 12 of these. Abnormalities of the thymus cannot be considered as a constant feature in this disease. Lymphoid deposits occur when the thymus is normal; they cannot, therefore, be considered, at least in all cases, as secondary to thymus disease. The presence of disease of the thymus gland in 10 cases of the 180 reported, while not a constant factor, yet occurs sufficiently frequently to be considered in a causal relation to at least one group of these cases. Of the 10 cases recorded, simple persistent enlargement of the thymus was found in 4 cases (in 2 of these associated with hemorrhages and an absence of eosinophiles in the thymus). Lymphoidal enlargement of the thymus was found in 4 cases and abscess of the thymus in 2 cases. Malignant disease elsewhere in the body was found in 4 cases. The lymphorrhages here described are not confined to the muscle system, but have been found in the heart, liver, thyroid, and kidney.

Nervous System.—The examination of the central and peripheral nervous system by the best methods and most skilful observation has given, as a rule, negative results. The presence in a small number of cases of slight degenerative changes in the ganglion cells and capillary hemorrhages in the cerebral gray matter have been considered as agonal. Lymphorrhages in the posterior root ganglia in one case may be considered as accidental as regards the location in the nervous system, and in no sense concerned in the production of the disease. From both a pathological and clinical standpoint the presence of lymphorrhages in otherwise normal muscles presents a valuable means of diagnosis in a suspected case. After extensive control work they have been found in other conditions only on one occasion, in a case of amyotrophic lateral sclerosis. In this disease there is, however, an associated degeneration of the muscle fibers, with a degeneration of the lateral tracts and gray matter of the spinal cord. The more recent work supports the statement of Buzzard, that his "experience affords reasonable grounds that lymphorrhages are constantly present in the muscles and other organs in cases of myasthenia gravis." Their detection, however,

entails a most thorough and diligent search of large numbers of sections, and the mere cursory examination of a few sections of muscle tissue is not sufficient. In one of the writer's cases a more extended reëxamination of some muscle tissue revealed the presence of small lymphorrhages.

Much speculation and relatively little accurate knowledge as to the cause of the disease is to be found in the literature. The consensus of opinion appears to be that the disease is due to some toxic agent. Weichardt has shown that physical fatigue in the normal individual is caused by the production of a toxin in the muscles. This toxin, however, cannot be demonstrated in the circulatory blood. If the toxin which he has isolated be injected into animals, an antitoxin is produced which is found in the circulating blood and acts *in vivo* and *in vitro*. He has also shown that the toxin of excessive fatigue may cause death. It would appear that the preservation of muscle excitability is dependent upon a period of rest either for the removal of the toxin from the muscle, or the production of an antitoxin in the blood which counteracts the fatigue toxin. Inasmuch as this toxin cannot be demonstrated in the circulating blood, the method of its removal from the muscle is not altogether clear. Link believes that the lymphorrhages in the muscles interfere with the lymphatic circulation, and thus prevent the removal of the fatigue products. This theory, of course, assumes the presence of lymphorrhages in the muscles early in the disease. Another view is that the toxin is not due to a disturbance of metabolism, but is of an exogenous nature, the result of some bacterial infection. The supporters of this view point to the presence of an infectious process in the history of a large percentage of cases, and to the fact that the infections are such, scarlet fever, typhoid fever, influenza, etc., as are not infrequently followed by a toxic neuritis.

The presence of the myasthenic reaction is the best evidence that the toxic action affecting the nervous system is not restricted to the upper motor neuron. The fatigue exhaustion produced by the faradic current and its similarity to that produced by voluntary muscle exercise would point to the muscular or intramuscular neuromechanism as the seat of derangement. It would appear from the experiments of Buzzard that the myasthenia is due to an exhaustion of the nerve end organs. In a well-marked case of myasthenia gravis, a moderate galvanic current was applied to the biceps muscles and a contraction obtained. The muscle was then faradized until it gave no response to a strong stimulus. Then it was tired out by making the patient flex the elbow against resistance exerted until all power of flexion was lost. On applying the same strength of galvanic current as used at first, an excellent contraction was obtained. Finally, on again applying the faradic current the muscle was found to be still unresponsive. The peculiar muscular phenomena in this disease, such as are demonstrated by this test, can perhaps be best explained by the work of Botazzi, confirmed later by Iotezko. They hold that in the muscles there are two contractable substances, a fibrillar and protoplasmic, giving different electrical reactions. The fibrillar substance gives a quick, lightning-like response, such as is produced on the normal muscle by the make or break of the galvanic current, whereas the reaction of the protoplasmic substance is slow and such as is seen in a degenerated muscle. Both substances react to the galvanic current, but the protoplasmic substance requires a much stronger stimulus than the fibrillar. A selective poison acting more on the

protoplasmic and reducing its excitability, would explain the exhaustion after a faradic or voluntary fatigue, whereas the muscle would still react to the galvanic current by the stimulation of the fibrillar substance. This theory relieves the peripheral nervous system of much of the responsibility that has been placed upon it in the production of myasthenia gravis.

Assuming the disease to be of toxic origin, a very natural query is as to its nature. The view above stated as to the exogenous origin as the result of bacterial invasion has little to support it other than the presence of an infectious process at the onset in thirty-nine cases, and an analogous condition as the result of a toxin in diphtheria and influenza.

The theory of an endogenous toxin, originally proposed by Weigert, has been supported by the more recent investigations in the pathology of the disease. He held that in Graves' disease and Addison's disease a definite internal secretion was necessary to the maintenance of bodily health; persistence of a secretion from a gland (the thymus) whose function in a normal individual should be in abeyance likewise gives rise to metabolic intoxication manifested by myasthenic symptoms. The experimental work of Link, who transplanted a thymus from one rabbit to another, showed negative results. Svehla found that the intravenous injection of an extract of thymus gland produced a fall of blood pressure, which he believed to be the outcome of vasomotor paralysis, and that large doses caused dyspnœa, collapse, and death. According to this theory, an excess of secretion would account for the attacks of dyspnœa and sudden death not infrequently met with in this disease.

This theory, of course, applies to the group of cases in which the thymus was found diseased. It would not apply to the cases in which the thymus rest is found in a normal condition. A large number of cases in which disease of the thymus is not present may be explained (assuming that the thymus is a lymphatic structure) by possible lesions of the lymphatic system elsewhere than in the thymus gland. This is supported to a certain extent by the presence of lymphoid collections (lymphorrhages) in the heart, liver, and kidney.

In this connection it is of interest to note that an identical syndrome to that of myasthenia gravis is seen in cases of myeloma in which the bone marrow is extensively involved (Senator).

Inasmuch as the lymphorrhages are not present in the affected muscles in a sufficient number of cases to account for the disturbance of function, we are forced to regard them as the physical manifestations of some underlying intoxication of unknown origin. The work of Spriggs on creatinin elimination is of interest in this connection.

Symptoms.—The symptoms of the disease are almost entirely confined to the muscular system. After a single muscular effort the muscles show decided fatigue, and, if the effort is continued, paresis, or even complete paralysis, results. After a period of rest the muscle returns to its normal condition. After a night's sleep the affected muscles may present a relatively normal condition; but, with the fatigue incidental to a day's routine, a moderate or even a marked degree of weakness is presented. This condition is most marked in muscles such as the elevators of the eyelids and the muscles of the jaw, which are maintained in more or less constant action during waking hours. The voluntary muscles throughout the entire body may be affected. The muscles supplied by the bulb, however, are

PLATE XVI

FIG. 1



The ptosis of the right eye is not so great as that of the left The photograph was taken one or two minutes after the glasses were removed. At times he is able to open both eyes fully.

FIG. 2



The eyeballs are almost completely covered. The photograph was taken after the glasses had been removed three or four minutes.

Myasthenia Gravis. (Case of Spiller and Buckman.)

From the *American Journal of the Medical Sciences*, April, 1905.

those which are most frequently and earliest involved. The symptomatology may be restricted to this group of muscles throughout the entire course of the disease.

Bulbar Muscles.—The disease, as a rule, is of slow onset, and begins with an involvement of the levator palpebræ superioris. The lids show a tendency to droop as the day progresses, until at nightfall the eye may be entirely closed. While ptosis, as a rule, is bilateral, it is not unusual to find it more marked on one side. Until the disease is well advanced, the drooping of the lids is entirely or almost entirely absent after a period of prolonged rest. In the advanced cases a well-developed or even complete ptosis may be present even after sleep. The other eye muscles, both intrinsic and extrinsic, the orbicularis palpebrarum, and the occipitofrontalis may also be affected.

Diplopia due to weakness of the external ocular muscles is a frequent symptom. It was noted as an initial symptom in thirty-one cases. The type of diplopia presented is fairly characteristic. In successive examinations, even at short intervals, there is a marked variation in the position of the images. This is due to the varying type of palsy as a result of the exhaustion of the different eye muscles during the progress of the tests. The weakness of the eye muscles and the relative loss of muscular balance give rise to irregular, jerky movements when the eyes are deliberately moved in one or other direction during examination. This condition has been mistaken for a true nystagmus. The convergent movement of the eyes, although at first fairly good, is easily exhausted. As a result of this, reading becomes impossible on account of the blurring of the print. The inequality of the pupils and a loss of reaction of the pupils to light has been noted in a few cases. A sluggish reaction of the pupils to light is of more frequent occurrence. The sphincter iridis does not show the fatigue reaction to repeated light stimuli. Hippus has been recorded in one case, but inasmuch as it is a frequent condition in other functional neuroses, no significance can be attached to it. The involvement of the upper muscles of the face, the occipitofrontalis and orbicularis palpebrarum, in association with the ptosis gives rise to a fairly characteristic position of the head. An isolated bilateral ptosis is partially or completely compensated for by contraction of the occipitofrontalis muscles. When this latter group of muscles is also affected, the advancing ptosis can only be compensated for by throwing back the head in an attempt to see under the lids. When the muscles of the neck become involved, it is impossible to maintain this backward position of the head, and it then not infrequently takes a forward paralytic position, resting on the chest.

Other ocular symptoms have occasionally been noted. Gunn, in one of Buzzard's cases, noted an associated dilatation of the pupils with elevation of the lids under emotional stress, although the patient was not able to deliberately elevate the lids by a voluntary effort. Von Graefe's symptom has been reported in several cases, and Stelwag's in an isolated case. Both these symptoms are not infrequent in tuberculosis and in exacerbations of chronic alcoholism. They may be considered as significant of an underlying intoxication. Several cases of myasthenia gravis have been reported in patients suffering with Graves' disease.

Involvement of the muscles of the lower facial distribution results in a loss of expression, an inability to pucker up the lips or whistle, a drooping of

the angles of the mouth, and drooling. It also gives rise to the so-called "nasal smile."

The muscles of mastication and deglutition, including the tongue, may be affected relatively early, or the involvement may follow in order of regular progression after the eye and face muscles. It was present at the onset of the disease, in association with eye symptoms, in four cases. The power of mastication may be slowly lost, as during the progress of a meal, or it may survive only the first attempt at chewing the food. The loss of power of the tongue may interfere with the transmission of the bolus of food to the pharynx. When the muscles of the palate are involved, liquid food may regurgitate through the nose. In advanced cases of myasthenia of this group, weakness becomes continuous throughout the entire day. When the power of deglutition is retained, the power of mastication can be assisted by the use of the hand. Clonic movements of the muscles of the jaws are occasionally noted. In one case this was so severe as to awaken the patient from a sound sleep. The difficulty in deglutition may become so serious as to necessitate the use of the stomach tube or alimentation by rectum. Choking attacks are not infrequent, and may be a cause of death either from interference with the respiration or from exhaustion.

The laryngeal muscles show fatigue manifestations similar to those noted in the extra-ocular muscles. The laryngoscopic picture is not at all constant, and varies from time to time. The pharyngeal reflexes are usually absent. Anæsthesia of the pharynx and larynx has been noted in two cases. Fatigue manifestations in the tongue are associated with fibrillary tremors. The speech is usually indistinct, and when fatigued has the nasal, mumbled character of true bulbar paralysis. In moderately advanced cases there is a paretic element which is not seen in true bulbar cases. The speech fatigue is accentuated in cases with involvement of muscles of respiration.

Involvement of the chest muscles becomes a very serious symptom. The respiratory excursion is very markedly diminished. Sudden attacks of dyspnœa often terminate the life of the patient. They occur usually toward the end of the day, or after exertion. It is not, however, always a fatigue dyspnœa, and may occur suddenly without any apparent cause. Strümpell considered a paralytic condition of the tongue to be an important factor in one of his own cases, and relieved the condition by pulling the tongue forward. Pneumonic infections are not infrequently a cause of death. They may be considered as due to lowered resistance to infection, or as inspiratory pneumonia. Cardiac distress may be present in association with or independent of dyspnœa.

The other muscles of the trunk may become so weakened as the disease progresses as to render the patient unable to sit up in bed. In some cases the terminal paralysis becomes so marked as to render the patient completely helpless.

Extremities.—These may become involved early, may remain free throughout the course of the disease, or they may be involved in the general paralytic phenomenon. The muscles nearest the trunk are the earliest affected, although the reverse may be true. When the hand muscles are involved, the handwriting shows the characteristic fatigue and a rapid loss of regularity in letters as the writing progresses. In the lower extremities the fatigue manifestations are usually noticed first in the iliopsoas and quad-

riceps muscles. Giving way of the legs may be a relatively early symptom. While the patient at first is able to walk fairly long distances, this power is rapidly impaired, until finally there is inability to walk at all. In relatively early cases the fatigue manifestations disappear after a short period of rest.

Myasthenic Reaction.—The electrical examination of the muscles gives important data for the diagnosis of the disease. If a rapidly intermittent current be applied to the affected muscles, there is at first a good, strong contraction; this contraction, however, is not maintained as in a normal muscle, but rapidly decreases until there is no response. If the current is intermitted for a short period of time (from one to two minutes), a strong response is again obtained, which disappears, however, more rapidly than the first. This test is called the *myasthenic reaction.* The rapidity with which the muscle becomes exhausted depends to a degree on the myasthenia present in the affected muscle. In advanced cases, the exhaustion may be complete within twenty to thirty seconds. In early or mild cases, only a relative degree of exhaustion may be obtained, even with strong currents. The reaction is not necessarily a constant one, and may be different from time to time, dependent upon variations in the course of the disease. It is influenced by the degree of fatigue in the muscles examined. It may be present in muscles supplied by one branch of a nerve and absent in other muscles supplied by the same nerve (Goldflam). After exhaustion of the muscles by the faradic current, a fairly good contraction may still be maintained by voluntary effort. The return of irritability after exhaustion is much more rapid than in normal muscle exhausted by fatigue (Murri).

The reaction to the galvanic current shows only a relatively slight degree of diminution of contraction. The exhaustion of the muscle is not here produced as with the use of the faradic current. In a questionable case reported by Kojewnikoff, the reactions of degeneration were present in the muscles of the tongue, which also showed atrophy. Atrophy of the tongue was found in five cases. In ten cases a relatively slight degree of atrophy was noted in the affected muscles.

Reflexes.—The reflexes of the extremities, as a rule, are exaggerated. Exhaustion of the quadriceps muscle either by fatigue or by faradization has no effect on the knee-jerk. Ankle clonus is never present, and the plantar reflex was uniformly of a flexor nature, *i. e.*, there was no Babinski reflex. In advanced cases, the jaw-jerk is usually absent. The skin reflexes are normal.

Negative Symptoms.—There is no disturbance of sensation. After exercise a sensation of stiffness or aching in the limbs may be present. This sensation is also present in advanced cases due to inability to move the affected parts. In rare instances the muscles may be sensitive to deep pressure. Buzzard reports a case of anæsthesia of the trunk, which he ascribes to lymphorrhages in the posterior spinal ganglia.

There is, as a rule, no atrophy or fibrillary tremors of the affected muscles (exceptions noted above). There is no trophic changes in the bones or skin. The visceral and rectal sphincters are never involved.

Mental depressive states have been noted in two cases.

Urine.—Spriggs, in a series of comparative experiments, found that in a case of myasthenia gravis the creatinin output, both absolutely and relatively to the total nitrogen, was definitely diminished, while that of uric acid remained normal.

Diagnosis.—The diagnosis of myasthenia gravis should never be a difficult matter if the regular symptoms are kept in mind. A combination of motor symptoms, progressive weakness and rapid fatigue of the voluntary muscles after exertion, and particularly the muscles supplied by the bulb, the presence of the myasthenic reaction and the absence of wasting, fibrillary tremor or sensory disturbance, with a retention of bladder and rectal control; of slow, more or less interrupted onset, running a variable course with a tendency to improvement and relapse, constitutes a characteristic symptom complex which cannot well be mistaken for any nervous or mental disease. The conditions from which it must be distinguished are true bulbar palsy, pseudobulbar palsy, diphtheritic paralysis, poliencephalitis superior, the muscular dystrophies, hysteria, and general asthenia.

True bulbar paralysis affects the lower distribution of the face, the tongue and the muscles of deglutition, by preference; the upper facial distribution and the ocular muscle are rarely affected, and then only in the advanced stages of the disease. There is marked atrophy, fibrillary tremors, and the absence of the myasthenic reaction. In pseudobulbar paralysis, the upper facial distribution is not affected, and the history of repeated apoplectic attacks will make the diagnosis clear.

Diphtheritic paralysis is of more rapid onset, and there is a history of the throat infection. The electrical reactions in the extremities will easily differentiate this from myasthenia gravis.

In poliencephalitis superior the onset is sudden. The headache, fulness in the head, and other symptoms of an inflammatory type are associated with constant paralytic phenomena of the ocular muscles, which bear no relation to fatigue.

The facioscapulohumeral type of muscular dystrophy may bear a striking superficial resemblance to the disease under discussion. The presence of muscular dystrophy in other members of the same family, the rapid wasting, the relative freedom of the muscles of deglutition, and the absence of myasthenic reaction should make the diagnosis easy.

In hysteria associated with neurasthenia the fatigue symptoms may be so marked as to bear a striking resemblance to myasthenia gravis. Sooner or later in the course of the disease, transient sensory disturbances, reversal of the color fields, headaches, and other painful phenomena, all of which may be influenced by suggestion, will lead to the diagnosis.

The intense asthenia following prolonged infection, such as typhoid fever, etc., need only be mentioned.

Prognosis.—The prognosis in the majority of cases is unfavorable. The disease must always be considered as a serious affection, with a possible fatal termination. Of the 180 collected cases, 72 proved fatal. These statistics, however, are, to a certain extent, misleading on account of the tendency in case reports to consider only fatal cases. Of the 5 cases which have come under the writer's observation, only the 2 which resulted fatally were reported. On the other hand, there is a disposition to report cases after a short observation without waiting a reasonable time to follow the course of the disease. In the fatal cases, the duration varied from one and one-half to two years. The disease may run an acute course, and in one case terminated in fourteen days. In another recorded case the patient lived fifteen years. It is impossible to state the percentage of cases that go on to permanent recovery. It is probable, however, that a permanent

cure often takes place. Respiratory failure with attacks of dyspnœa should be considered a grave symptom. Sudden death in such cases is not of infrequent occurrence. The disease varies markedly in its course and in its symptoms. Even in apparently favorable cases unaccountable relapses are likely to occur.

Treatment.—All possible infectious or toxic causes should be, as far as possible, removed. In puerperal cases, septic or toxic processes in the genito-urinary apparatus should receive particular attention. The advisability of the removal of tumors must depend upon the particular case and the location of the tumor.

A full or modified form of rest treatment is indicated. The whole therapeutic regime should be so directed as to eliminate all possible muscular fatigue. The diet should be so arranged as to secure the best nutrition with the least effort in mastication, and in severe cases a full milk diet is indicated. In the earlier cases food should be so prepared as to avoid the necessity of mastication fatigue. If the use of the stomach tube should at any time be deemed necessary, either for purposes of diagnosis or alimentation, the greatest care should be used. Death may result from the fatigue and excitement incidental to the use of the tube, or as the result of attacks of choking. Unless the tube is taken easily and without excitement or gagging, its use should be avoided.

Care should be taken to properly protect the patient from cold. In those cases in which the symptoms are aggravated or induced by cold weather, a warm, equable climate should be recommended. Electricity should only be used for purposes of diagnosis, and even then only with the greatest care. Faradism as a therapeutic agent does harm and galvanism does no good. When massage is used, it should be given only for a very short period of time and the effects carefully noted. It is likely to do more harm than good. The glandular extracts (suprarenal, thyroid, and thymus) have been tried without appreciable results. In one case (Buzzard's) thyroid extract with strychnine gave excellent results at first, but the patient relapsed while still taking the thyroid extract.

General tonics would appear to be indicated, and in conjunction with hygienic measures have given good results. Arsenic in the form of Fowler's solution, the iron preparations, and strychnine in small doses have been recommended. Strychnine has been used in massive doses without distinct benefit.

PARAMYOCLONUS MULTIPLEX.

Paramyoclonus multiplex is an affection first described by Friedreich in 1891, and characterized by clonic, lightning-like contractions occurring either constantly or in paroxysms, affecting at times all the muscles of the body with the exception of the eye muscles, but more frequently the muscles of the lower extremities.

Etiology.—The cases reported have been chiefly in males. Some emotional disturbance, such as fright, is often the determining factor. In pure cases hyperirritability of the nervous system, such as is seen in tuberculosis, is often present. Tuberculosis has been reported as present in certain cases.

Pathology.—Of the three cases which have come to autopsy, the case of Hunt showed hypertrophy of the muscle elements. Friedreich stated

that the condition was due to an increased irritability of the gray matter of the spinal cord with an irregular discharge of motor impulses. That the disease is one of the lower motor neurons or of the muscles is accepted. Irritation of the motor cortex does not give isolated muscular movements. Localized contractions of muscles or individual fibers of muscles have always been considered as having a localization in the gray horns of the spinal cord. We would, therefore, conclude, in view of negative findings in the nervous system, that the disease is the result of some disturbance of function of the inferior neuromuscular mechanism.

Symptoms.—All of the muscles of the body may be affected. The muscles of the extremities, and especially of the more proximal portion, are those most usually affected, in the upper extremities the biceps, triceps, and supinator longus, and in the lower extremities the internal vastus, external vastus, the rectus, and the adductors. The muscles affected display the greatest activity, the individual muscles in use springing forward in contraction with the greatest rapidity, as if suddenly irritated by galvanic shock. These contractures are not associated, as a rule, with fibrillary tremor. They do not usually produce any motor response in the extremities. Occasionally a barely perceptible involvement of the arm may be the result of the more violent contractions. The intensity and rapidity of the contractions may be increased by mechanical irritation of the skin, mechanical irritation of the muscles, exposure to cold, and by excitement. They are usually decreased by voluntary motion, although the contrary may be true; they usually disappear during sleep. Occasionally, as in Friedreich's case, the patient may be frightened out of sleep by a sudden very painful crampy movement of both legs, resulting in a sudden jerking of these members against the abdomen. The electrical irritation of the muscles is normal and the reaction of the muscles to mechanical irritation is not increased. There is no disturbance of sensation, no atrophy of the affected muscles, and no cerebral, spinal, bladder, or rectal symptoms.

Diagnosis.—The symptomatic picture of a well-defined case of paramyoclonus multiplex is distinctive. This term has been used so frequently, however, to designate other forms of myospasm, that considerable difficulty has been experienced in limiting the disease as a clinical entity. There is no question that most of the cases reported in the literature should not be considered as such in the strict sense of the term. It should be remembered that a myokymia or contraction of individual groups of muscular fibrillæ is not uncommonly present in neurasthenia and other functional nervous disorders. The fibrillary tremor of wasting muscles need only be mentioned in this connection.

Dana, in 1903, differentiated the cases recorded as paramyoclonus multiplex into the following groups: (1) Paramyoclonus multiplex of Friedreich; (2) myoclonus of the functional or hysterical type; (3) myoclonia of the convulsive tic type; (4) myoclonia of the degenerative chorea or familial, or myoclonia epilepsy type; and (5) myoclonia of the infectious and symptomatic choreas.

There should be no difficulty from a careful study of the case in excluding cases of the second group. The contractures are not strictly fibrillar, but are of the coarse, irregular, clonic type, associated with minor or more extensive movement of the extremities. There are other evidences of hysteria usually associated, and this is more particularly true in the early

stage of the disease. The muscular phenomena are not constant, and the frequency of the attack is influenced by excitement, excessive attention, etc.

The cases belonging to the third group (convulsive tic type) are easily differentiated as representing a disturbance of cortical origin as differentiated from the spinal type seen in paramyoclonus multiplex. All movements belong to the purposive group of gross movements. There are no fine, fibrillar tremors of the muscles, but a quick, jerky contraction of the muscle groups, such as blinking the eyes, screwing up the face, twisting the head, shrugging the shoulders, etc. In Tourette's disease (maladie de tic convulsif) this purposive type of muscular spasm may be widespread and affect the muscles over the entire body,

The myoclonus epilepsy of the fourth group is easily differentiated from paramyoclonus multiplex by the presence of epileptic attacks. It is a manifestation of excessive functional disturbance of the cortex. The movements do not resemble paramyoclonus multiplex so much as they do those seen in Sydenham's chorea. They are, however, prone to be rhythmical and associated with some fibrillary tremors. A case of this kind occurring in the writer's service at the Philadelphia Hospital was at first mistaken for chorea insaniens, on account of the presence of mental symptoms following an epileptic attack. In this case there was epilepsy in other members of the family. From the infectious chorea group, Sydenham's chorea, etc., this disease is easily differentiated by the gross purposeless character of the movements in the latter disease. From the electrical chorea of Dubini it is distinguished by the presence of the severity and fatal character of the latter affection. In Dubini's disease the rapid rhythmic movements are very violent, as if produced by an electric shock, and may be associated with fever, paralytic symptoms, epileptic convulsions, and atrophy and wasting of the muscles.

Prognosis.—The prognosis in true cases of paramyoclonus multiplex must be considered unfavorable. The cases reported in which such startling curative results were obtained by the use of electricity are usually looked upon as cases of hysteria. The disease usually lasts a long period of time, unless, as not infrequently happens, the life of the patient is terminated by some intercurrent affection such as pulmonary tuberculosis.

Treatment.—Careful attention should be paid to associated visceral disease, more particularly of the lungs. If the patient is under weight, a modified rest treatment with overfeeding is indicated. Careful attention should be paid to keeping the gastro-intestinal tract in good condition. The urine and stools should be carefully watched in order to insure proper elimination through these channels. Flushing of the system by the use of large quantities of water in the dietary and by the occasional use of Epsom salt will be found in some cases to be of assistance. The bromides, chloral, and the valerianates have been used for their calming influence on the central nervous system. They have a distinct value in controlling excess symptoms of a functional and at times of an hysterical nature. Arsenic is of value in some cases. Thyroid extract has been used in this disease, but its value has not been established. Various forms of electrical treatment have been lauded as curative agents. The galvanic current, the static spark and breeze have been reported as producing valuable results. They at least offer a helpful means of eliminating the excess of functional symptoms present in most of these patients.

PERIODIC PARALYSIS. FAMILY PERIODIC PARALYSIS.

Definition.—A flaccid paralysis affecting the muscles of the trunk and the extremities, temporary in character and recurring at more or less regular intervals.

History.—Beginning with a case reported by Cavaré[1] in 1853, several cases may be found in the literature, among them two cases by Gibney,[2] practically all of which were considered as due to malaria. Schachnowitsch,[3] in 1882, reported a case of intermittent paralysis in a patient whose father was similarly affected. Our knowledge of the disease as a clinical entity began with the detailed study and consideration of a case by Westphal and Oppenheim[4] in 1885. While this was a sporadic case, the careful study led to investigation and reports of family groups by Cousot,[5] Goldflam,[6] and Bernhardt[7] in Europe, and Taylor[8] and Holtzapple[9] in America.

Etiology.—Judging from the list of cases reported in the literature, this is a rare disease. Most of the cases reported have been in family groups. 5 cases have been reported by Cousot, 22 by Goldflam, 2 by Hirsch,[10] and 11 by Taylor. Mitchell[11] reports one group in which 4 and another in which 5 were affected. Holtzapple reports 17 cases.

That heredity is an important etiological factor in these family groups, there is no question. In Holtzapple's series, cases in four generations in the same family were studied. While a neurotic basis for the disease is generally denied, migraine was present in 10 of the 17 cases reported. Five had attacks of paralysis and headache. Thirteen other members of the family suffered from headache. In some of the cases the headaches preceded the attack, developed in early childhood, and disappeared with the development of the paralytic phenomena. In other cases the headaches continued, alternating with attacks of paralysis. This, however, is the only group of cases in which migraine is of etiological importance.

[1] *Gaz. des Hóp.*, 1853, No. 89 (*Aus. der Gazett. med. de Toulouse*) (Quoted by Taylor).

[2] Intermittent Spinal Paralysis of Malarial Origin, *American Journal of Neurology and Psychiatry*, 1882, i, 1.

[3] *Wratsch. Russisch.*, 1882, p. 537 (quoted by Taylor). Ref. in *Goldflamztschft f. klin. Med.*, 1891, xix, supplementary volume, p. 240.

[4] Ueber einen werkwürdigen Fall von periodischer Lähmung aller vier Extremitäten, mit Gleichzeitigem, Erlöschen der electrischen Erregbarkeit während der Lähmung, *Berl. klin. Woch.*, 1885, Nos. 31, 32, p. 489.

[5] Cas de paralysie périodique, *Bull. d'Acad. de Méd. de Belgique*, 1886, No. 7, also *Rev. de Méd.*, 1887, vii, 190.

[6] Ueber einen eigenthümsliche Form von periodischer, familiarer warscheinlich auto-intoxicatorischer Paralyse, *Zeit. f. klin. Med.*, 1891, xix, supplementary vol., p. 240; *Wien. med. Presse*, 1890, Nos. 36, 37, 38, 39, p. 1414; *Deutsche Zeit. f. Nervenheilk.*, 1897, xi, 242; *Zeit. f. klin. Med.*, 1891, xix, supplementary vol., p. 240.

[7] Notiz über die familiäre Form der Dystrophie muscularis progressiva, und deren Combination mit periodische auftretender paroxysmaler Lähmung, *Deut. Zeit. f. Nervenheilk.*, 1896, p. 111.

[8] *Journal of Nervous and Mental Disease*, 1898, xxv, 637, 719.

[9] *Journal of the American Medical Association*, 1905, xlv, 1224.

[10] Ueber einen Fall von periodischer, familiarer Paralyse, *Deut. med. Woch.*, 1894, No. 32, p. 646.

[11] A Brief Report of the Clinical, Physiological, and Chemical Study of Three Cases of Family Periodic Paralysis, *Brain*, 1902, xxv, No. 1, p. 109.

The disease may develop as early as the fifth year, but, on the other hand, may not appear until after thirty.

Transmission may occur either through the male or female. Individual members of the family may be entirely free. These may, however, transmit the disease, the affection in this manner skipping a generation. In Holtzapple's cases, migrainous headaches were present in members of the family who did not have the disease. In this very interesting family the disease seems to have started from the father of the first generation, who suffered from periodic sick headaches. The statement of Taylor that these cases have occurred in families of unusual nervous stability and that in no case do we find evidence of a degenerative family is not borne out. The attacks in some of the cases were most frequent during the cold months. This is of especial interest in connection with the article of Rich,[1] who described a condition of tonic spasm of the face muscles in five members of his own family, due to exposure to cold or dampness, in one case there being a complete general paralysis with the exception of the tongue, as the result of sleeping in moist underclothing. While the paralysis, being of the nature of a spasm, is different from the flaccid palsy of periodic paralysis, the influence of cold in its production is of interest. Sinkler[2] also reports a sporadic case of recurrent facial paralysis extending over a period of ten years, without such etiological factor. Muscular exertion, lack of exercise, indiscretions in diet, exposure to a draft, menstruation, constipation, nervous or mental fatigue, worry, and emotional excitement have all been given as conditions which precipitate an attack.

Pathology.—Two of the patients in Holtzapple's series have come to autopsy but no lesion which could be associated with the disease was found (Winternitz). Small portions of muscles have been excised and studied by Goldflam and Oppenheim. The former found a waxy degeneration to which he attributes no importance. The latter found an increase of the diameter of the individual muscle fibers, hypertrophy of the fibers, rarefaction of the primitive fibrillæ with vacuole formation. To these changes Goldflam attributes qualitative, electrical, reactive changes which he alone found in the free intervals between the attacks. These changes, apart from the value to the subject under discussion have a special significance when studied with the cases of Bernhardt, which showed from early childhood a persistent and constant loss of power in certain muscle groups, separate and apart from the periodic attacks which develop later. Both of these authors would place the disease on the basis of the muscular dystrophies.

In the absence of any such condition in the other cases reported, the prevailing idea is that we are here dealing with an auto-infection of unknown origin, associated with a lowered condition of metabolism and induced by excessive muscular activity, followed by a period of rest. Extensive investigation of the urine and the blood has not given much information as to the nature of this intoxication. Goldflam and Taylor reported a lymphocytosis with a moderate eosinophilia. In Mitchell's case a study of the toxic effect of the blood serum by an intravenous, intraspinous, intrameningeal, and intraneural injection, gave inconclusive results. The same was true as to

[1] A Unique Form of Motor Paralysis due to Cold, *Medical News*, Phila., 1894, xv, 210.

[2] Discussion on Taylor's paper. Vide *Journal of Nervous and Mental Disease*, 1898, p. 744.

the alkalinity of the blood, and examination of the urine for acetone and diacetic and lactic acids. A low ammonia content of the urine was found with an extremely low creatin elimination, especially accentuated immediately preceding and during the paralytic attack, with a sudden rise to the normal immediately following the attack. From this the authors conclude that "the symptoms in this case are not solely due to the retention of creatinin or creatin, but that the attacks are due to metabolic disturbance, and that this disturbance may be situated chiefly or primarily, perhaps entirely, in the muscles themselves."

Holtzapple found a diminished excretion of urea, and that the worst sufferers were those who showed the most marked diminution in the average daily output of urea. One of his patients showed a very marked increase in the elimination of urinary solids and urea during the attack.

Schlesinger in an isolated case found acetonuria in the majority of the attacks, and occasionally albuminuria and hyaline casts.

Goldflam, from a study of the injection of urine into rabbits, isolated certain substances, the effect of which, when injected into animals, was not conclusive. He found, however, that the injection of urine taken during the attack seemed more toxic than that of a free interval.

A study of the reported cases suggests a close analogy of the muscular phenomena of the disease and those of myasthenia gravis. In some cases of myasthenia gravis, attacks of paralysis lasting a few days, resembling those of periodic paralysis, are seen.[1]

The rapid exhaustion of the muscular power and the failure of the muscles to respond to the faradic current are suggestive. A careful study of the thymus gland, which is found so frequently diseased in myasthenia gravis, has not been made. A more complete knowledge of the functon of the thymus in childhood and in disturbances associated with persistent thymus in adult life, might throw some light on both these subjects.

A study of the series reported by Holtzapple bring this whole group of cases into close analogy with periodical ocular paralysis associated with migraine. This series of cases, in which migraine plays such a prominent part and which is not found in any of the other family groups, may be considered to be a connecting link between the periodic family palsies and the periodic oculomotor palsies. In the latter group, a partial or complete oculomotor paralysis of one side, lasting a few days, a week, or longer, is associated with attacks of migraine with a tendency to recurrence at fairly regular intervals. There is a partial or complete oculomotor paralysis affecting one or all the muscles supplied by the third nerve. In cases of this condition which have come to autopsy, a disease process of the third nerve has been found, *i. e.*, in one case a plastic exudate, and in three others tumor formation. Stryzeminski differentiates a functional and an organic form. Oppenheim agrees with Charcot upon a vasomotor basis for the oculomotor palsy, and considers it to be due either to a vascular cramp giving rise to an ischæmic form of paralysis, or a paralysis of the vessel nerves leading to compression by dilatation of the vessels. This would explain the temporary paralysis without damage to the nerve and a terminal degeneration when

[1] Collins, in discussion of Taylor's article. Vide *Journal of Nervous and Mental Disease*, 1898, p. 745.

the condition is frequently repeated. In a patient of the writer's with migraine, recurrent hemiplegia attacks, lasting from a few hours to a day and recurring from time to time in association with attacks of migraine, autopsy showed hemorrhagic capillary extravasation in the distribution of the middle cerebral artery.

Holtzapple, following Westphal, explains his cases on the ground of a "vasomotor neurosis affecting the blood supply to the anterior horns which are supplied almost wholly by the anterior spinal artery," and the terminal paralyses "to a slow degeneration of the anterior horns due to frequent disturbance of nutrition and the atrophy of the muscles due to involvement of the trophic cells." That such local vascular conditions can exist was shown in a case of migraine, examined by the author with Harbridge, in which the temporary collapse of the retinal vessels could be seen with the ophthalmoscope.

While the association of this one extensive group of cases with migraine points strongly to a central vascular causation, the muscular phenomena noted during the period of paralysis do not support this view. This would bring the disease within the grouping of poliomyelitis, and to a certain extent confirm the opinion of Dana of a recurrent poliomyelitis. Isolated cases in childhood of a flaccid paralysis with loss of reflexes which last only a few days and then disappear, are not infrequently seen and are usually considered as an abortive or evanescent type of poliomyelitis. The objection to this view and to the other theories of a central nature of the affection is the complete loss of reaction of the muscles during the attack of paralysis to galvanic and faradic stimulation. This would indicate an involvement of the terminal distribution of the nerves in the muscles and the muscle fibers themselves. As a matter of fact, the loss of the myotactic as differentiated from the nerve irritability, together with the changes in the metabolism, point to the muscles rather than to the nervous mechanism. Oppenheim would explain this on the grounds of a peripheral disturbance in the circulation. Malaria as a cause was suggested in the early cases on account of its periodicity, but has not been confirmed by later studies of the blood.

Symptoms.—The clinical picture presented is so striking as to be almost dramatic. The patient, as a rule, retires to bed feeling perfectly well, or with slight prodromal symptoms, and awakens during the night with a flaccid motor paralysis which may involve all the voluntary muscles except those of the face, eyes, tongue, the organs of speech and of deglutition. This paralysis may last from a few hours to a few days and disappears gradually or rapidly. In the most severe cases the paralysis is complete and involves the muscles of the trunk and of all four extremities. The muscles of mastication and the tongue muscles may be partially involved. While there is no paralysis of respiration, and while the respiratory rate, as a rule, remains within the normal range, there is often an inability to take a deep breath, and the breathing may be somewhat embarrassed, due to an accumulation of mucus in the throat and bronchial tubes. Bladder and rectal functions are retained.

The paralysis is flaccid; the deep and superficial reflexes of the paralyzed muscles are lost. In one of Holtzapple's patients prodromal increase of reflexes was recorded. There are no disturbances of objective sensation. Subjective sensory phenomena are sometimes present; formication, numbness, a sensation of heaviness may precede and continue during the attack.

A feeling of soreness of the muscles is not infrequently complained of after the attack passes off.

In Holtzapple's patients, a bulimia commonly preceded the attack, and if the appetite was satisfied, and more particularly by an indulgence in rich or heavy food, an attack was almost certain to follow during the night. Other persons in the same family were not so affected. While prodromal symptoms are not uncommon during the day, the paralytic phenomenon develops, as a rule, during sleep. The affected individual awakens during the night to find himself absolutely helpless as a result of paralysis affecting all four extremities, the trunk, and the neck. Sleep may not, however, be interfered with, the paralysis first manifesting itself on awakening in the morning. In other cases the patient awakens before the attack is fully developed, and many hours may elapse before the paralysis is complete. In some cases the paralysis may develop during the waking hours. In these cases incoordination of the hands and even unconsciousness may usher in an attack. After a period of paralysis varying from a few hours to a week, motor power gradually returns and with it a return of the reflexes and of myotactic irritability.

While there is no paralysis of the bladder or rectum in the strict sense of the term, it is the exception to have urine voided or the bowels moved during the attack. This is probably due to a diminution of secretion and excretion. This is borne out by the examination of the stomach contents in a case of Edsall's. "Even starch digestion was not proceeding and there was a total anacidity, showing the whole digestive process to be absolutely at a standstill and the gastric motor power diminished, or abolished for a time." This also explains the lack of desire for food during the attack. During convalescence from the attack one or two loose bowel movements or vomiting may occur.

The temperature remains normal throughout the paralytic phenomenon. The pulse may be normal in frequency and volume or may be weak and irregular, with evidence of cardiac dilatation. Schlessinger[1] reports a case in which there was bradycardia with cardiac arhythmia during the attack. The electrical reactions have been carefully studied during the attacks and in the intervals, by Oppenheim, Goldflam, and others. In severe attacks there is complete loss of reaction to the faradic and galvanic currents. In the interval between the attacks there may, in some cases, be a diminution in the reaction, a slow vermicular reaction of the muscles, and other evidence of degenerative change. Continued over a long period of time, these muscles may show degenerative atrophy. In most cases in the interval between the attacks the electrical reaction returns to normal.

Besides the severe form of the disease above described, many cases present a less intense grade of the affection both in distribution and the extent of the paralysis. When the paralysis is localized it is most frequently confined to the lower extremities. Paralysis of the upper extremities, the neck, the face, and a hemiplegic form have been described. In some of the cases, and most frequently the localized forms, there may be only a partial paralysis with slight or marked loss of power. Such attacks may be evanescent, lasting one-half to one hour, or may be prolonged as in the major attacks. In these cases the deep reflexes may be diminished or lost with

[1] *Wien. klin. Woch.*, 1905, No. 13.

retention of the superficial skin reflexes. There is likewise a diminution and not a complete loss of reaction to the electrical current.

Abortive and equivalent attacks may occur. In the abortive attack there may be a heavy, sleepy, tired feeling, with slight weakness in the extremities, not sufficient, however, to incapacitate, extending over a period of several days. In some of Holtzapple's series, migraine attacks alternated with the paralytic phenomena and were sometimes associated with it. Consciousness was preserved in all the cases reported, with one exception, in which an attack of unconsciousness ushered in the paralysis (above noted).

Between the attacks the patient feels, as a rule, perfectly well. In some cases the patient may awake in the morning completely paralyzed, and yet be occupied with laborious work by afternoon of the same day. In other cases the attack passes off more slowly, the full power not being restored in from twenty-four to forty-eight hours. In Burr's case it lasted an entire week.

Course.—While cases have been reported as early as the fourth year and as late as the thirty-first year, the majority of the cases develop about the age of puberty. There is a tendency to a diminution in the frequency and intensity of the attacks after middle life. A degenerative type of paralysis affecting both upper and lower extremities and confining the patient to a wheel-chair developed in some of Holtzapple's cases. While this affection is considered by all the other observers as not dangerous to life, sudden death in an attack occurred in six of Holtzapple's cases,[1] giving a mortality of 35 per cent. in his individual group.

Treatment.—A study of the family groups above mentioned suggests the idea that the underlying factors in the production of the disease varies somewhat in the different groups, and this is borne out by the results of treatment. In two of Mitchell's cases the bromides give no results; in one it had some slight influence. In Holtzapple's cases, 0.5 dram of potassium bromide with 1 or 2 grains of caffeine citrate, repeated in one or two hours, had a decidenly abortive influence when taken in the early paroxysms. In not a single instance did he note the development of an attack when the bromide had been taken during the onset.

In Mitchell's cases citrate of potash in doses of 45 to 60 grains a day had "some small but uncertain effect." Administered in the beginning of a seizure in repeated large doses, it shortened and mitigated the paralytic period.

Colon lavage, intestinal antiseptics, venesection, hypodermoclysis, and various forms of electrical treatment have been tried with negative results. A study of the factors which determine the attacks and their elimination as far as possible from the life of the individual, together with the maintenance of the physical and nervous tone at the normal level, would appear to be the most rational treatment of a disease which remains with us as it began with Westphal, an unsolved riddle.

[1] The examination of the cord and nerves from one of these patients by Winternitz (Johns Hopkins Hospital) did not show any lesion to account for the symptoms.

PART V.

VASOMOTOR AND TROPHIC DISORDERS.

CHAPTER XXVII.

RAYNAUD'S DISEASE.

By WILLIAM OSLER, M.D.

Definition.—A vascular change, without organic disease of the vessels, chiefly seen in the extremities, but also occurring in the internal parts, in which a persistent ischæmia or a passive hyperæmia leads to disturbance of function or to loss of vitality with necrosis of the parts. This definition excludes the cases of necrosis due to obliterative arteritis, and the cases of postfebrile and of multiple neurotic skin gangrene.

Introduction.—The blood supply of all parts is controlled by the vasomotor mechanism, which regulates the amount by varying the calibre of the arteries. The centre of control is influenced by various stimuli, central (cerebral), visceral, and external. The sudden blush of shame, the instantaneous pallor of fear, indicate the extraordinary rapidity of action, and illustrate, moreover, the extremes of vascularity in the skin. In health the vasomotor reactions are not subject to great variations, and so far as the skin is concerned the alterations in its vascularity are dependent more on external temperature than anything else. So, also, in the internal organs, there are certain physiological changes in the blood supply associated with periodic functional activities. The regional control of the circulation is analogous to that of a central distributing station in a great irrigation system, with its elaborate system of telephones to and from all the plantations. A uniform supply may be given to all, or the various streams may be diverted to a supplementary reservoir; any local plantation may be flooded at a moment's notice, or the supply may be cut off to the finest rivulets.

In the skin, one of the most vascular of parts, the blood supply varies greatly in health, particularly in the degree of normal distention of the vessels of the exposed parts. Whole nations are pallid, others are rubicund. There is an antagonism between the amount of pigment and the degree of permanent distention of the vessels of the skin. The darker Latin races have not nearly the same rich blood supply to the face and hands as the fair Teutonic people. How rarely one sees in France or Italy the full complexion of the English. In individuals heredity and constitutional

peculiarities have an important influence on the cutaneous blood supply; occupation, too, is a factor of the first moment, as persons who constantly work in the open air have a permanently heightened skin vascularity. As is well known, the grade of the vascularity is no indication of the amount of blood in the body—there may be anæmia with a red face, and a chronic pallor may be present, with a normal blood count.

In health the color of the skin is singularly constant—what we speak of as a person's complexion is the mean between the vascularization and the amount of pigment. But there are a great many individuals with what may be called an unstable skin circulation—the vasomotor mechanism is not under good control, but works badly, so far as the skin is concerned; that special plantation, to use again the analogy of the central irrigation scheme, is too apt to be flooded, or the supply may be cut off abruptly. How many persons, healthy enough in other respects, are constantly worried by an abnormal filling of the vessels of the face, sometimes permanently, but more often intermittently, the result of central, emotional causes. Or the vessels of the hands may be constantly congested from an instability of the vasomotor mechanism.

By far the most common vascular skin reaction is to cold, in which we see four phenomena of the first importance in the study of Raynaud's disease. A hand exposed to a very low temperature is at first flushed, then gets blue, and finally begins to grow pale; the radial artery may be felt to get small and the pulse more and more feeble. At first the anæmia may be patchy, as though some capillary areas had greater resistance, but soon the hand is of a dead white color, less sensitive than normal, and stiff from inability of the muscles to move freely. This bloodless condition, due to spastic contraction of all the vessels, is called *local syncope*. Continued exposure at a very low temperature may result in a freezing of the whole hand. Brought into the warmth, the blood gradually returns to the parts, a backward flow takes place from the veins, as a hand which has been frozen may become gorged with venous blood before a radial pulse is perceptible. It grows livid, mottled, and swollen; pressure with the finger causes a spot of anæmia, but the return flow is sluggish and almost imperceptible. Pain begins at this stage—the stage of *local asphyxia*. If the hand has not been exposed for a very long period this venous stasis gradually disappears. The radial pulse begins to be more distinct, the lividity is less intense, and the finger imprint is more quickly obliterated. Soon the fingers begin to throb, and the whole hand aches, and within half an hour or less the color is a vivid pink, the arteries are throbbing and large, and a pulse may be felt in every finger, and the capillary pulse is visible in the nails —this is the stage of *active hyperæmia*. But if the hand has been exposed for a very long time and frozen hard, the venous stasis which follows the thawing does not disappear, the fingers remain livid and cold, the circulation does not become reëstablished, and *necrosis* or *gangrene results*.

Raynaud's disease is a condition in which these four phenomena of frostbite, singly or together, are experienced *without frost*, sometimes, indeed, as a result of exposure to cold, but more frequently due to unknown internal causes, which bring about precisely similar vascular reactions in the fingers or toes, ears, and nose. In a majority of healthy persons the vasomotor mechanism works very smoothly and the reactions are within narrow limits; but many people have naturally, or acquire, a great instability of

this system, so that abnormal reactions follow slight stimuli. S. Solis Cohen has called this condition vasomotor ataxia, and it is just in these individuals with an imperfect control of their irrigation pipes that we see the phenomena of Raynaud's disease. The morbid flushing and blushing, the vascular erythism of Basedow's disease, the transitory erythemas of the neurasthenic, the arterial spasm in migraine, in certain types of angina pectoris, and possibly the vascular crises in many abdominal conditions (lead colic, tabes, angioneurotic œdema, etc.) all come under this vasomotor ataxia, either of the dilator (paralytic) or constrictor type. A scratch with the finger nail, a line drawn, say, on the skin of the chest or abdomen, is followed by a very slight reaction, usually a fine red line, but in the subjects of vasomotor instability one of three reactions follows; the most common is an intense hyperæmia on either side of the line, 4 or 5 mm. or more in width, which lasts for ten or more minutes, and is sometimes associated with a widespread erythema of the adjacent skin. This is the characteristic vasodilator reaction, and it is always an active, never a passive, hyperæmia. Much less common is it to see, following the irritation, a white line, a band of anæmia 4 or 5 mm. in width, which results from spasm, vasoconstriction, of the small arterioles of the skin. It may disappear gradually or it may be followed by an active hyperæmia. These two reactions, dilator and constrictor, represent the two vascular skin reflexes, which are as important to test as the knee reflex or the big-toe reflex, as they give an indication of the existence, degree, and type of vasomotor ataxia. The third and rarest reaction is the exudative, when in the line of the irritation, serum is poured out from the hyperæmic vessels with the production of a wheal, factitious urticaria (dermatographia).

Historical Note.—So striking a phenomena as symmetrical gangrene did not escape description until 1862, the date of Raynaud's first paper. The affection is called by the name of the distinguished French clinician, because he gave the best account of it, and a rational explanation of the cause. "I propose to show that there is a variety of dry gangrene affecting the extremities which cannot be accounted for by vascular obstruction; a variety characterized by a remarkable tendency to symmetry, affecting always similar parts of the upper or lower limbs, all four at once, in certain cases the nose and ears, and I shall try to show that this form of gangrene has its origin in a disturbance of the innervation of the capillary vessels." This was the object of Raynaud's thesis, published in 1862; a second important paper appeared in 1874 (*Archives gén. de méd.*). Both have been translated and edited by Barlow for the New Sydenham Society, 1888. The article by Barlow in the first edition of Allbutt's *System;* the monograph on the disease by T. K. Monro, Glasgow, 1899; the *Index Catalogue* of the Surgeon-General's library, and Cassirer's *Die Vasomotorish-trophischen neurosen*, Berlin, 1901, give the literature, old and new. Monro's book is the best critical study of the disease, and is a storehouse of facts relating to it.

Etiology.—It is not a common disease. Among 23,000 medical patients admitted to the Johns Hopkins Hospital in a period of about twenty years there were only 19 cases. Cassirer collected 168 cases from the literature for his monograph (1901) and Monro 180 cases for his work (1899). The last-named author estimates that about 1 case occurs among 3000 patients.

Nationality.—The disease appears to be more common in England and France than in Germany. It is not rare in America, as our figures show. It is relatively more frequent among Hebrews.

Sex.—Women are much more frequently affected than men—62.5 to 37.5 per cent. in Monro's series—and this holds good for both mild and severe forms.

Age.—More than 60 per cent. of the cases occur between the tenth and the thirtieth year. In Cassirer's statistics there were 22 cases under five years of age; from five to ten, 8; from eleven to twenty, 25; from twenty-one to thirty, 40; from thirty-one to forty, 27; from forty-one to fifty, 28; above sixty, 18. A number of cases have been described in children. Friedel saw a six months' old child attacked with swelling of the back of the hand; gradually the fingers of both hands became blue and necrosis of the tips of several of the terminal phalanges occurred (Cassirer). True Raynaud's disease is rare in the aged, and some of the cases reported have been of senile gangrene from endarteritis. F. P. Henry reports the case of a woman, aged seventy-seven years, who had typical attacks involving the nose, ears, and extremities.

Family Disposition.—In a number of cases several members of the family have been affected. In the milder forms it is not uncommon to see dead fingers in three or four sisters. I know one family in which the mother when young had recurring attacks of "white and blue fingers," and her three daughters have been greatly annoyed with vasomotor disturbances of the hands and feet. In Colman and Taylor's patient the grandfather and the great uncle had Raynaud's disease. Cases of symmetrical gangrene have been reported in sisters (Makins) and in three brothers (Bramann).

Psychical Disturbances.—To a sudden shock, or a fright, the symptoms have been assigned in a number of cases. Nervous, highly strung individuals are certainly more prone to the disease. Some of the worst cases have been in hysterical patients.

Sexual disturbances were thought by Raynaud to play an important part. In some patients mild attacks have been more likely to come on at the menstrual period. In one instance the disease followed directly upon pregnancy (Dickinson). Sexual excesses have been thought to be of moment.

Cold and Damp.—The milder forms are much influenced by climate and by the weather. Cases of local asphyxia are much less common in America than in England, where severe chilblains leading to superficial necrosis represent a frequent type of the disease. Cold has an important influence, and there are cases in which the symptoms only occur in the winter, and, as a rule, patients liable to attacks are always worse in cold weather. On the other hand, a patient of Raynaud's was always worse in the summer. Washing the hands in very cold or in very warm water may bring on an attack.

But in a considerable number of the cases no factor of any moment can be determined—the disease begins in healthy individuals, and the actual cause remains obscure; in a majority, however, there is a marked neuropathic disposition, an instability of the nervous system, or an actual perversion as in the hysterical cases.

Infectious Diseases.—In many acute and in a few chronic infections multiple gangrene occurs, but it is of a different type to that of Raynaud's diseases and should not be included in this category. In malaria, typhoid

fever, measles, and scarlet fever local areas of necrosis may occur in various parts of the skin; in a few cases acrocyanosis has preceded the local gangrene of the finger tips, but, as a rule, the distribution is very different, the skin of the trunk or of the limbs, the lips, and the cheeks.

In syphilis true Raynaud's disease may occur, but many of the cases of gangrene in the affection are due to arteritis. A remarkable case of Raynaud's disease in congenital syphilis is quoted by Cassirer: A two-year-old child with hereditary lues after exposure to cold had attacks of cyanosis of the hands and feet, and subsequently of the ears, which had also spots of local necrosis. Recovery followed mercurial treatment. Monro's figures give only 2.8 per cent. of cases with syphilis.

Arteriosclerosis.—Vessels beginning to be diseased seem particularly prone to spasm, and a certain proportion of cases of true Raynaud's disease show widespread arterial changes, but a sharp distinction should be drawn, when possible, between the local gangrene due to obliterative arteritis and that which follows the protracted asphyxia of Raynaud's disease.

Nervous Diseases.—Gangrene occurs in a whole series of organic affections of the nervous system—neuritis, many affections of the spinal cord, acute and chronic, and in hemiplegia. These various forms of local gangrene, some of which bear a striking resemblance to Raynaud's disease, will be discussed in the section on diagnosis.

Morbid Anatomy and Pathology.—No characteristic changes have been found. After a critical review of the autopsies which have been made, Cassirer concludes that we have not, as yet, any sufficiently thorough study of all the parts in a typical case. Not one of the negative cases has been of such a typical nature, nor has the examination been of so exhaustive a character as to justify the statement that there is no anatomical basis in the disease. The positive results consist either of changes in the bloodvessels or in the nervous system, singly or combined, but none of these are in any way peculiar or constant. Neuritis has been found in several very carefully studied cases (Pitres and Vaillard, Wigglesworth, and others), but it is impossible to say whether it was causal or a complication of the disease itself. Changes in the cord have been reported, but the cases have not always been genuine instances of Raynaud's disease, and we shall refer under the diagnosis to the conditions in the central nervous system, which may induce vasomotor and trophic disturbances. Endarteritis has been found in some genuine instances of long standing, in others the vasomotor changes have been due to the chronic disease of the arteries, and the cases do not come in the category of Raynaud's disease. Endarteritis, endophlebitis, and degeneration of the nerves have been found. And lastly, the examination has been negative in a number of carefully studied cases.

The *pathology of the disease* lends itself to theoretical discussion. The key to it is found in a study of the effects of cold in the vascular system. The mild and severe types correspond to chilblains and frostbite. Every feature of the disease is mimicked by the effect of cold in the extremities, and we know cold itself is one of the potent factors in inducing the recurring attacks. We have already studied the sequence of vascular events when a part is exposed for a long time to a low temperature, the vasoconstrictor effect on the arteries, capillaries, and veins producing local syncope, which may itself pass into necrosis; but more commonly a vascular reaction takes place, the blood flows back from the veins, and a state of asphyxia or cyanosis

follows. From this, one of two events may result: if the part has not been long exposed, as the tip of the nose or an ear in ordinary mild frostbite, the asphyxia gradually disappears, the arteries begin to dilate, the parts get red, and a state of intense hyperæmia follows, with pain and throbbing, and no necrosis results; on the other hand, if the part has been exposed for a long time, no vascular reaction takes place, the local cyanosis remains, the circulation is not rëestablished, and necrosis or gangrene results. We have seen that constrictor and dilator influences pass from the controlling centres to every vascular territory of the body, and they may be excited by mental, external, or somatic stimuli. There are persons in whom the centres controlling these vasomotor actions are unstable—the machinery of the irrigation centre is in charge of an inexperienced official who has not learned to work the sluices in proper response to the telephonic demands; he turns a full head of water into one of Mr. Epidermis' farms and forgets all about it, or he shuts off the supply from another, flooding the one, parching the other, and unless a call gets through in time to correct the mistake, death of the crops is the result. This is exactly what happens in Raynaud's disease. The centres are at fault and work imperfectly. We have seen that the reaction to external cutaneous stimuli is very varied, usually vasodilator but often vasoconstrictor, which is the more important of the two in Raynaud's disease.

One cannot predict in an individual case when the skin is irritated whether the response will be constrictor or dilator. It has been suggested that when the *white line* of anæmia follows there is disturbance in the suprarenal metabolism, but of this there is no evidence, and a prolonged study has convinced me that its only indication is a morbid sensitiveness of the vasomotor centres. In the local syncope of a finger or of the hand widespread constrictor influences pass to the subsidiary centres, controlling the circulation of the part, and the arteries, capillaries, venules, and veins are thrown into a state of spasm. The contraction of the arteries may be felt (in the radial) and seen (in the retinal arteries); the spasm of the veins may be seen and has been observed by Barlow and others in cases of Raynaud's disease. The spasm of the capillaries is probably a sort of "squeeze" on the part of the bloodless tissues, and possibly the muscle fibers of the skin itself may be affected. The dead white, cold finger contains not a drop of blood, and is as exsanguine as if a small Esmarch bandage had been applied. Suddenly the sluice gates are opened and there is a rush of fluid into the empty channels, every stream is full, every pipe gorged to bursting. When you take off the Esmarch bandage from a finger, so rapid is the inundation that the eye can scarcely follow it. And this is what happens when the local syncope gives place to the active hyperæmia. The flushing is rarely so sudden, but a dead white finger may become hyperæmic in from twenty to thirty seconds. The ischæmia and the active hyperæmia are readily explained—we see them every day as the effect of constrictor and dilator influences.

The local asphyxia is another matter. In frostbite, active hyperæmia, cyanosis, syncope is the order; the cyanosis follows a transient flush of hyperæmia seen as the first reaction to the cold. In Raynaud's disease the order is usually syncope, asphyxia, hyperæmia. In frostbite it seems clear that the asphyxia is due to a backward flow from the veins, to which the local syncope yields as the part thaws, before the arteries passing to the part can

be felt to pulsate. The asphyxia of Raynaud's disease may be due to the same cause; contraction of the veins has been seen by Barlow and by Weiss, but that was when the asphyxia already existed. But the first thing must be the relaxation of the spasm of the venules and veins to permit of the blood entering the empty capillaries. The stasis and cyanosis persist so long as the arterioles and arteries remain in spasm. In moderate grades of asphyxia some little blood trickles through the sluice gates, but in the deep purple skin of a typical example of Raynaud's disease the circulation has ceased and death of the part is imminent. The necrosis is a simple matter, as simple as if a string is tied tightly about the finger tip.

The cause of this instability of the vasomotor centres, the nature of the change in them, the reason of the symmetrical distribution, an explanation of the associated hæmoglobinuria—these are questions awaiting solution. With a clear-cut symptomatology, having affinities with other affections due to angiospasm, the disease must not be confounded with a series of other disorders which have with it gangrene as the most striking feature.

Symptoms.—*General Description.—Mild, moderate,* and *severe types* of cases may be recognized.

(*a*) **Mild Forms** (*formes frustes*).—A girl, aged seventeen or eighteen years, subject, perhaps, for years to cold hands and cold feet, begins to have tingling in the fingers and toes, and finds that on exposure, or when the weather is cold, her hands and feet get very blue. When she comes into the house they throb and ache, get red and hyperæmic, and feel tense and swollen. It may take hours before they are normal. During successive winters these symptoms may be repeated, and the condition is regarded, and rightly so, as chilblains. There is nothing to distinguish it from scores of cases of this common affection, but one day, following perhaps a longer exposure to cold or after a week or two of cold weather, in which she has had to work in a room insufficiently warm, the cyanosis is more persistent, the skin over the knuckles swells and turns black, blebs form, and half a dozen or more areas of superficial necrosis occur. The knuckles may be the only parts affected, or the extreme tips of the fingers. The patient may be incapacitated for a week or two, and a series of attacks may come on with changes in the weather. Winter after winter the trouble may recur, and, while never reaching a high grade, and only causing very superficial necrosis, the suffering and incapacity may be very great. In the cold, damp climate of the British Isles such cases are common. England is the land of chilblains, mild and severe, owing to the damp cold and to the insufficient heating, particularly of schools and institutions. Cold in itself is not the only factor, else these vasomotor disturbances would be more common in Canada, where, on the contrary, they are rare. If of transient duration, cold hands and cold feet have not the same import as the all-day-long lividity of these parts caused by working in rooms at a low temperature.

The "beefsteak" hand, a source of great annoyance, often of discomfort, is a permanent vasomotor disturbance, met with chiefly in young girls. While there are cases that persist throughout life, the condition may be transitory and associated with menstrual disorders. I have twice seen it with the slight hypertrophy of the thyroid gland of puberty. The color varies with the outside temperature—either cyanotic or hyperæmic. The hands may be permanently swollen, and the cold, clammy feeling is very disagreeable. The hands alone may be affected, more often hands and feet, and there may be

the "beefsteak" cheeks with permanent dilatation of the small veins, which are sometimes unpleasantly distinct. There are men of full habit, often of gouty stock, who have this same permanent engorgement of the bloodvessels of the extremities and of the face in a degree that passes the limits of health. In the winter the cyanosis may be extreme, and when there is much exposure the hands become very stiff and there may be numbness and tingling. In these cases it is a question altogether of cyanosis or hyperæmia, not of local syncope; the extremities are either blue or red, not white, and they do not come into the category of the *formes frustes;* but there is a mild type of the disease, in which all these vascular disturbances recur in remarkable sequences. On the morning of the opening of the Johns Hopkins Hospital a young woman applied who presented in a typical manner the vasomotor changes of Raynaud's disease. The fingers alone were affected, and usually only in the daytime. Without any warning they would become "dead," and, as she expressed it, "go to sleep;" sometimes three or four of one hand or two of one and one of the other—never the thumb. The stages were always pallor, a dead white, which would last an hour or longer, and then the finger became cyanosed, and afterward of a vivid red, and the throbbing became unpleasant. The fingers were often in different stages, and when I first saw her the middle finger was of a dead white, in local syncope, the ring finger was cyanosed, while the little finger was red and in a state of intense active hyperæmia. She was a nervous girl, much overwrought mentally, and this condition had been a source of great anxiety. The attacks had occurred at intervals for several years, but the cyanosis had never persisted long enough to cause local necrosis of the finger tips. I saw this patient at intervals for many years, often in most typical attacks, but necrosis never took place, and she gradually got quite well.

In middle-aged women, in connection with the paræsthesia and numbness of the hands and feet—the acroparæsthesia—there may be vascular changes, sometimes dead fingers—syncope most often, and slight grades of cyanosis.

(*b*) **Moderate Severity.**—A woman, aged twenty-five or thirty years, after perhaps a period of worry and ill health, begins to feel pain in the fingers or in only one or two fingers of each hand. Or it may be only a numbness and tingling, not actual pain, and the fingers feel stiff. Then she notices that they have changed in color, are white and cold, and remain so for an hour or two at a time, gradually getting red and warm. Within a day or two a change occurs—they remain permanently blue, asphyxiated, perhaps to the second joint. The pain becomes more severe, and may require morphine. The tip of one finger or the terminal joint of another gets darker, and perhaps a few small blebs form. The other fingers show signs of restored circulation, but necrosis has occurred in the pad of one and in the terminal inch of another. The eschar of the pad of the finger gradually separates and healing takes place, with much less loss of tissue than had been anticipated. The necrotic phalanx shows a line of demarcation, and after a couple of weeks the bone is snipped off, but it takes a couple of months before healing is complete. The general health improves and the patient gets quite well. She may never have another attack, or, what is more common, in six months or a year there is a second. In many of these cases of moderate severity after two, three, or even four slight attacks complete recovery takes place.

(*c*) **Severe Forms.**—No more terrible malady exists than the severe type of Raynaud's disease. A man, aged twenty-five or twenty-six years, of a neuropathic disposition, begins to have numbness and tingling in the hands and feet, with local syncope. The feet become painful, and one morning he notices that they are livid to the ankles, slightly swollen, and so tender that he cannot put them on the ground. At the same time the ears become swollen and red, with the margins very blue. The tip of the nose changes in color; within a few days the cyanosis has deepened, the toes are black, the feet purple, and about the ankle is a zone of a bluish red color; it looks as if both feet would become gangrenous. A black line has formed at the margins of the ears and there is a small black spot at the very tip of the nose. The pain in the feet is atrocious. Pulsation is felt in the arteries. About the end of ten days the feet begin to look better, the circulation is reëstablished as far as the bases of the toes, which remain black, and a line of demarcation begins to form. Instead of losing both feet, only two or three toes of each foot may be lost, and a small rim of the ear and a superficial abrasion of the tip of the nose. Within three or four months the patient is well. The greatest difficulty has been in the separation of the necrotic parts. The following winter the patient notices that the urine is bloody; the fingers begin to feel stiff and painful, and in a few days an attack is in full swing; this time he loses a finger or two. Three months later, before the hands have quite recovered, the right foot gets cyanotic and painful, the lividity extends above the ankle, and the gangrene is so extensive that the leg has to be amputated. For a year there may be good health, and suddenly the other foot becomes affected, the gangrene extends, and this leg, too, is lost. After a six months' respite the unfortunate victim may have an attack of such severity in the hand that the arm has to be amputated. I saw a woman who had had just this sequence and had lost within five years one hand and both legs. The attacks had begun in the fingers like the ordinary type of Raynaud's disease. In a few cases serious internal complications occur. The hæmoglobinuria persists and the patient may die of it, or there may be attacks of severe abdominal colic. Cerebral symptoms may recur with each attack in the extremities, epilepsy, aphasia, transient hemiplegia, and the patient may die in coma. Fortunately, these very severe forms are exceptional, and yet in attendance at every large hospital there is usually one case of this sort, and the maimed victim finally drifts into an almshouse.

The Symptoms in Detail.—The local *syncope*, the first stage, is the most characteristic single symptom of Raynaud's disease; the others, cyanosis, active hyperæmia, and gangrene, we see in many conditions; but the *dead white anæmia* of a finger, of a toe, of one ear, is a rare phenomenon. Occasionally, in arteriosclerosis one sees spasm of the peripheral arteries and pallor of hand or foot, but such a persistent ischæmia as that seen in typical cases is not met with in other pathological states. The fingers are most often affected, then the toes, the ears, and the tip of the nose. The whole foot or hand is not often involved. The anæmia may be induced in a few minutes, giving a dead white appearance to the skin. At first it may be patchy and gradually extends. Areas of slight discoloration may be seen before the ischæmia is complete. Once fully established the finger looks "dead," and is cold and sometimes clammy like the finger of a corpse. The temperature may be 20° to 30° below that of the adjoining finger or of the palm of the hand, and the part feels cold. The patient may com-

plain of numbness or a heavy, painful feeling, sometimes of pins and needles. At this stage the pain is rarely extreme. The motility is impaired, and on attempting to move it the finger feels stiff. The duration of the ischæmia is very variable—from a few minutes to an hour or more—very much less than the cyanosis or active hyperæmia. The attacks may recur eight or ten times in a day. Mild grades of local syncope are often seen in the "dead fingers" of nervous and neurasthenic individuals, but the ischæmia is not complete, the color is not often of a dead white, and it is not associated with the reactions of the attack of Raynaud's disease. The paræsthesia may be marked, particularly in the cases of "waking" numbness. Occasionally in healthy persons local spasm of the arteries causes a patchy ischæmia of the skin. It is sometimes seen under emotional excitement, and Hochenegg mentions a case of a healthy man whose nose became of a chalky white color under excitement.

A good imitation of this condition may be had by making artificial anæmia of one finger with a rubber ring. Within a minute the temperature drops and there may be numbness and tingling. The sensation is not nearly so unpleasant as if the light ligature is placed around the finger while full of blood. A useful demonstration when lecturing on the disease is to produce the local syncope with a rubber ring rolled up the index finger from the tip; tie a ligature tightly about the middle finger, and in a minute cyanosis will be present; then if the circulation is reasonably active there will be the pink skin of the ring finger in active hyperæmia, the cyanosis of the middle, and the ischæmia of the index finger. The local syncope may disappear in one of two ways—the taps may be turned suddenly and the vascular areas are immediately flushed with blood, just as happens when the ring of rubber is removed, the anæmia of the finger is instantaneously obliterated, but much more frequently it is a slow process, and a mottling appears and gradually the *second stage* of the process is produced.

Local Cyanosis or Asphyxia.—This has been called by various names—local apnœa, acrocyanosis, acro-asphyxia—but the first names are the most appropriate. This may come on without a previous stage of syncope; at any rate, syncope is not always seen. The color is variable, from a reddish blue to a blue black, sometimes an ashen gray, and if it persists for a long time, an intense indigo blue. The finger nails may be of an inky black color. There may be shades and mottlings of color from a light grayish blue to an intense blue black and an inky black. Pressure with the finger causes an area of anæmia which is very slowly obliterated. With the cyanosis the finger is swollen but not œdematous. The temperature is lowered—8° or 10°. Riva measured the temperature before the attack between the thumb and index finger at 35.8° C.; in the attack it was 20.6°, and that of the hollow of the hand 23.4°. Even in a warm bath the part may remain cold and cyanotic. The asphyxia may be intense in one finger while the adjacent one is in syncope. The color is due to the fact that the circulation is so slow that the capillaries are filled with red corpuscles, the hæmoglobin of which is deoxidized. Normally in the capillaries of the skin the circulation is so active that the corpuscles have not time to discharge their full load of oxygen, but when from any cause there is stasis the corpuscles unload all they possibly can and the change in color is noticed immediately. Two events may follow the local asphyxia—active hyperæmia or necrosis.

PLATE XVII

FIG. 1



FIG. 2



Raynaud's Disease, showing superficial gangrene.

FIG. 3



Raynaud's Disease, showing superficial gangrene of one toe.

Active hyperæmia is an important stage in Raynaud's disease. It may follow directly upon the syncope, more often it follows the asphyxia. After persisting for several hours, or even for a day or more, the color begins to change, the patient feels a throbbing, and gradually the circulation is restored and the cyanosis is replaced by a bright pink. The finger gets hot and throbs, the pulse is to be felt in it; the radial is full and large, if the hand has been affected, and a capillary pulse may be seen in the nails. This stage lasts a variable period, usually bearing some proportion to the duration of the cyanosis. While the sequence of white, blue, and red is the rule, there are exceptions; the process may begin in one finger with a transient hyperæmia, and then the syncope follows and the cyanosis, a sequence of red, white, and blue. Monro gives the case of a physician who had had various vasomotor phenomena and whose hands in the morning, after he had washed them, were very red, then they became white and afterward blue. When the hand and fingers are involved, all three processes may be observed together—the hand may be of a deep red, one finger white and the others cyanotic, or adjacent fingers may be red, white, and blue. Persons subject to attacks, particularly of the milder forms, may bring on an attack of local asphyxia by going out in the cold, when the hands become blue, sometimes at once, sometimes with a stage of preliminary syncope; then when in the warmth the active hyperæmia is quickly established and the hands get hot, throb, and are painful. If the asphyxia persists and the circulation is not reëstablished, there is danger of the final stage—*necrosis* or *gangrene.* This may follow the local syncope or more commonly the asphyxia. The fingers or toes or the whole foot remain cold and dead without any attempt at recovery of the circulation; the color grows darker and one or two of the fingers, or the tip of one, in mild cases, becomes black. Small blebs with serum form and break, leaving excoriations, or the bullæ break and leave a dry, black skin. The extent of the gangrene is generally much less than the appearance of the part would indicate; a foot which looks hopeless at the end of the first week may by the tenth day show great improvement and the toes alone be gangrenous. The necrotic part is gradually marked off by a definite line, and the skin of the proximal part is inflamed, often with a dull, cyanotic appearance. The process of separation of the parts is very tedious and accompanied by great pain. It may take weeks for a big toe to slough off and months for the anterior part of a foot. When the sloughing reaches the bony parts it is well to help the process by surgery. In the ears the necrosis is usually very superficial, forming a black eschar along the edge of the helix. In successive attacks a considerable portion of the margins of the ears may be lost. It is rare to see much necrosis of the nose, and even when the asphyxia is very pronounced and gangrene looks threatening, recovery may take place with a very superficial loss of substance.

Symmetrical parts are usually but not always involved. The process may begin in both hands or both feet and extend to gangrene in only one foot or one hand. When the ears are involved superficial necrosis occurs, as a rule, in both. A typical attack may occur in only one extremity. Of the distribution of the gangrene Munro gives the following figures: In 43 per cent. of the cases one or both of the upper extremities was attacked; in 24 per cent., the lower extremities, and in 22 per cent., upper and lower limbs. Parts other than the extremities may be involved; in severe attacks in which

the ears are affected the cheeks may be dusky red and swollen and threatened with gangrene. The chin may be the seat of local syncope or asphyxia. In rare instances the tongue is attacked. In Powell's case the tip became deeply cyanotic, and a superficial ulcer formed. The lips have been the seat of both syncope and asphyxia; the nates and the labia majora have been attacked. Raynaud describes a case of local and painful asphyxia of the nipples. The eyelids have been involved. The cases in which local gangrene occurs on the trunk and the proximal parts of the extremities are rarely Raynaud's disease, but the postfebrile and other forms. In a few cases the areas of local asphyxia may be present, as in Tannahill's remarkable case: A seven-year-old child subject to cold hands and cold feet had numerous attacks of local asphyxia of the extremities and of the ears, with hæmaturia, and later a severe attack in the left foot, with gangrene. The child had also well-marked local asphyxia in areas on the extensor side of the left forearm and one on the inner side of the leg.

Other Local Changes.—With recurring attacks of local asphyxia the hands may get thick and coarse. Rolleston describes a case in which they became visibly larger. Marked thickening of the skin of the fingers and a parchment-like induration may occur suggestive of scleroderma. In a few cases this disease has directly followed repeated attacks of local asphyxia. I have had a well-marked instance of this kind which is reported under the section on Scleroderma. The nails may be much altered in color, of a dark brown or brownish black, rough, ribbed longitudinally, and where partial necrosis of the phalanx has occurred they are greatly deformed. Suppuration may take place at the root and prove very obstinate. Desquamation of the skin of the fingers occurs if the cyanosis has lasted for a day or two.

Disturbances of Sensation.—Pain is an element of the first importance in all severe forms of the disease, particularly when the stage of gangrene is reached. The patient dreads to have the parts touched, or the slightest contact of the clothes causes agony. It is not confined to the affected parts, but may pass up the legs or arms, and may reach an intensity that causes the patient to cry out. Extreme local cyanosis may occur without much actual pain, and one rarely sees the pain of erythromelalgia unless necrosis has taken place. The worst attacks I have seen were in hysterical subjects and in very neuropathic Hebrews. In the severe attacks of local asphyxia the fingers may throb and ache as in chilblains. The local syncope may be painless, but in instances preceding gangrene the pains may be the first symptom and even antedate the ischæmia. Occasionally the whole course of the disease is painless. One of my patients lost the tip of one index finger without any pain, but in other attacks during the three years in which he was under observation the pain was often atrocious. In another case the index finger was not painful, only numb, but the adjacent middle finger, in very much the same condition and with one gangrenous bleb, was very painful; and after he recovered, although the pads of the two fingers looked very much the same, glossy and bluish white, that of the index finger felt only a little numb when touched, but the skin of the middle finger was exquisitely tender.

Anæsthesia, a dull numb feeling, is usual with the local syncope; paræsthesia, tingling, and prickling are present during the asphyxia, sometimes an unpleasant throbbing and burning. Following the attacks there may be

extreme hyperæsthesia of the affected fingers or toes, and for months the patient may not be able, for example, to use the hand, on account of the sensitiveness of the finger tips. The cases with dissociation of sensation are usually syringomyelia.

Sweating may be present in the stage of local syncope; the finger may be covered with a cold sweat. In the active hyperæmic reaction the whole hand may be moist, and in the protracted asphyxia a clammy moisture may cover the skin.

Motor Disturbances.—With the fingers dead and cold, motion is impaired, and they feel stiff, but, as a rule, there is not much motor disability apart from that caused by the pain. In a few cases wasting has been described in the interossei and in the thenars and hypothenars.

Complications.—If, as we suppose, the symptoms of Raynaud's disease are due to an angiospasm of the peripheral vessels, evidence of similar changes should occur elsewhere in the body, and in two regions at least, the eye and the brain, such is the case.

Eye.—Raynaud himself noticed that there were coincident alterations in the retinal arteries. In a man with typical attacks of local asphyxia, during the period of reaction, the central artery of the retina and its branches had very clear contours, and were definitely narrower around the papilla than at the periphery, and here and there was a sort of partial constriction; the veins were dilated, elongated, and pulsated. In another case Panas observed a definite relation between the state of the arteries of the fundus and the cyanotic attacks, contracted when the fingers were cyanosed, widened when they returned to their natural color. These are exceptional events; as a rule, there are no changes in the retinal vessels corresponding in any way with those in the peripheral arteries.

I have looked in vain for signs of constriction in several very typical cases, in one when the local syncope of the hands was extreme. In the two cases with marked cerebral symptoms there were no visible alterations in the retinal vessels. In a remarkable case reported by Weiss, with symmetrical gangrene of the fingers and reddening with superficial gangrene of the skin of the left side of the face in the zygomatic region, there was retraction of the eyeball in the same side, narrowing of the palpebral fissure, and slight ptosis, phenomena which Weiss referred to the cervical sympathetic.

Brain.—We have learned to recognize angiospasm as an important factor in cerebrospinal lesions. Sclerotic arteries are particularly prone to spasm, and the multiform clinical picture in certain cases of arteriosclerosis can only be explained by a transient contraction of the bloodvessels, causing an ischæmia and loss of function. The temporary amblyopia has been seen to be due to spasm of the retinal vessels, and the transient monoplegias, hemiplegias, aphasias, and even paraplegias, from which rapid and complete recovery takes place, cannot possibly be due to organic lesions, and are most likely the result of angiospasm in definite vascular territories. I have known twenty or more transient attacks of aphasia and monoplegia from which perfect recovery has taken place. Identical symptoms occur in Raynaud's disease. Raynaud himself reports a case in a woman, aged sixty-two years, but the transient hemiplegia occurred two years before the symmetrical gangrene. Weiss reports transient aphasia, and Simpson temporary hemiplegia, both in patients having well-marked features of

Raynaud's disease. One of the most remarkable cases on record came under my care at the Johns Hopkins Hospital.[1]

The patient, a woman, aged forty-eight years, was admitted with the complaints of difficulty in speaking and peculiar sensations in the fingers. For five or six years she had occasional attacks of numbness and mottling of the fingers. In April, 1891, she had dizziness and perhaps loss of consciousness. A month later there was a second attack, with pain and local asphyxia in the little and ring fingers of the right hand. In January, 1892, there was another attack of dizziness, with asphyxia and superficial necrosis of the terminal phalanges of the index and little fingers of the right hand. On February 2 there was an attack of aphasia, with loss of power in the right hand and paresis of the right foot. Recovery from this was rapid. On March 31 there was a second attack of complete aphasia and spasm in the right hand. After this she had good health until the summer of 1894, when there was slight pain and aching in the right leg and toes. In February, 1895, there was local asphyxia, with necrosis of the terminal phalanx of the middle finger of the right hand. On April 4 she had a severe attack, with headache and slight paralysis of the left arm and leg. There were severe local symptoms in the right hand and fingers. On July 19 there was a third attack of aphasia with hemiplegia of the right side, local syncope, and asphyxia of the right hand and fingers. In January, 1896, there was intense pain in the right hand, with rapid gangrene to the elbow; after this coma and death.

A somewhat similar case is reported by Dukeman: A woman, aged fifty-seven years, began to have local cyanosis and necrosis of the left ring finger. During the convalescence from this attack the fourth finger of the right hand became involved, and she had a right-sided hemiplegia and died in coma. It seems only reasonable to regard these attacks as due to vascular changes in the brain of the same character as those which occur in the peripheral vessels. True, the arteries of the brain itself have not been found in spasm, but the ephemeral character of the attacks can scarcely be explained in any other way, and we have the visible demonstration in the eye of the transient loss of function in connection with spasm of the arteries of the retina.

Epilepsy.—A number of cases have been reported in which convulsions have occurred; in some the epileptic seizures have been independent of the local cyanosis, in others the association has been very close. The case reported from my clinic by H. M. Thomas,[2] one of the most extraordinary in this respect, illustrates the wide symptomatology of the disease. A man, aged twenty-three years, had typical Raynaud's disease—fingers, toes, ears, nose—and the cyanosis often proceeded to superficial necrosis. The attacks only occurred in the winter; in the warm weather he was perfectly well. Epileptic attacks accompanied the outbreaks of local cyanosis, but only in the winter, when he also had hæmoglobinuria. We followed his case with great interest for more than three years. The local cyanosis was very marked, but the necrosis was never widespread. He lost a little of the ear margins, of the tip of the nose, and of the pads of the fingers. After three years the epilepsy ceased, but the winter attacks of cyanosis came on as

[1] *American Journal of the Medical Sciences*, 1896, cxii, 522.
[2] *Johns Hopkins Hospital Reports*, 1891, ii, 114.

usual and were associated with crises of abdominal pain, just like those of angioneurotic œdema, and he had swelling of the spleen. Unfortunately we lost sight of him.

Mental Troubles.—The subjects of Raynaud's disease are very often neurasthenic and subject to great depression. In hysterical patients, during the attacks the mental symptoms may be aggravated. There are no psychical disturbances peculiar to the disease. In a large number of mental disorders attacks of Raynaud's disease have been described—mania, amentia, melancholia, circular insanity, and progressive paralysis of the insane.

Organic Lesions of Brain and Cord.—Except the complications referred to above, there are no features of Raynaud's disease suggestive of coarse lesions of the central nervous system. On the other hand, local cyanosis and trophic disturbance are exceedingly common in many organic diseases of the brain and cord. These have often been described as cases of Raynaud's disease, but they are the vascular and trophic lesions well recognized as occurring in myelitis, syringomyelia, and tumor of the cord. These forms will be discussed under Diagnosis.

Urinary Changes.—*Hæmoglobinuria.*—Albuminuria may occur during the attacks in paroxysmal form, or it may be permanent. Actual nephritis is rarely present. Hæmoglobinuria is the most remarkable complication of the disease, and occurs in a considerable number of cases. It was first described by Jonathan Hutchinson, and has been specially studied by English authors. The well-known surgeon Druitt described his own case.[1] The attacks were brought on by worry or exposure to cold, and were associated with local cyanosis, numbness, and tingling of the extremities, and at times these features were suggestive of imminent gangrene. He died in 1883 of hæmaturia.

Monro, who deals very fully with this complication in his monograph, notes the peculiar fact that hæmoglobinuria is much more common in males. In Raynaud's disease only 37.4 per cent. of the cases are in males, but in the cases of hæmoglobinuria with Raynaud's disease the proportion is 71.4 per cent. of males. As a rule, the urinary changes are only met with during the existence of the local cyanosis, and the attacks are more liable to occur when the patient is up and about. When put to bed the hæmoglobinuria may cease, although the paroxysms of local cyanosis recur. The influence of cold is the most remarkable feature in the attacks; a patient may be free during the warm weather, as in one of the cases mentioned above, but with the onset of cold weather the attacks begin and may recur at intervals through the winter. As Barlow pointed out, this is exactly what happens in the cases of ordinary paroxysmal hæmoglobinuria. During the attacks the spleen may be enlarged. Abdominal colic occurred in my case. So far as I know, jaundice has not been described in these cases. Various changes in the blood have been described—hæmoglobinæmia with irregularity of the corpuscles and disinclination to form rouleaux. I do not know that the fragility of the corpuscles has been studied in these cases by the new methods, but we may suppose that from some unknown cause this has been greatly increased. The connection with the vasomotor phenomena remains obscure. Possibly in the cyanosed areas changes occur in the

[1] *Medical Times and Gazette*, 1873.

serum of the stagnated blood which give to it a foreign hæmolytic quality, but we have in reality no reasonable explanation of the remarkable phenomenon.

Skin.—In a few cases purpura has occurred. Urticaria has been present and has recurred with the paroxysms. The relation between true Raynaud's disease and scleroderma has been much discussed. Repeated attacks may give a hard sclerosed aspect to the fingers. It is certainly rare for generalized scleroderma to follow the recurring attacks of Raynaud's disease; there are a few cases, however, with this sequence. Barlow mentions a case with typical local syncope of the finger tips which ended in symmetrical gangrene of the tip of each index finger. She recovered, but the fingers presented an atrophied and contracted appearance; subsequently, extensive scleroderma of the skin of the chest walls came on and she died marasmic. I have reported a typical case of this kind. Much more commonly as the scleroderma develops on the hands and feet there is local cyanosis and trophic changes in the finger tips and in the knuckles. Local necrosis occurs, and the terminal phalanges become shrunken and contracted.

Heart and Arteries.—In a few cases organic heart lesions have been present. The extraordinary acrocyanosis of congenital heart disease never goes on to necrosis. Occasionally in mitral and tricuspid lesions in children the cyanosis of the fingers and toes may be remarkable, and in the cold the lividity may be extreme. Embolic gangrene has in some cases of organic heart disease been mistaken for Raynaud's disease; in others there appears to have been a combination of the two conditions, as in Colson's patient (quoted by Cassirer), a four-year-old child with an organic valve lesion. Sudden swelling of the left hand occurred with gangrene of the fingers. Three months later there was a second attack of swelling of the fingers of the left hand, with blueness, which disappeared in a few days, but at the same time the left ear became swollen and cyanotic. This seems to have been a case of genuine Raynaud's disease complicating a heart lesion.

Arteriosclerosis is not a common feature, but it may be present, and a number of typical cases have been reported. In a majority of the patients the arteries are healthy, and the pulsations may be felt in the vessels of the affected limbs even to the smaller branches. In long-standing cases definite changes in the arteries may be found. A patient of Barlow's had typical attacks of local syncope and cyanosis, and in his second winter a little gangrene of the second and third toes of the left foot. Two years afterward the toes of both feet became very blue and gangrene involved the left foot and ankle. Amputation of the thigh was done. The arteries were found to be diseased. The right toes showed signs occasionally of local asphyxia, and two years later the foot became gangrenous and necessitated amputation of the right leg. The arteries were found diseased. Barlow remarks that this case approximated to one of Friedländer's obliterative arteritis, and it seems reasonable to suppose that the recurring spasmodic contractions of the vessels brought about a permanent alteration in the walls and lumen. In the very large group of cases of local gangrene due to arteritis it is by no means easy to say whether the condition is one of Raynaud's disease or not.

Joints.—In recurring attacks in the fingers the terminal joints may be ankylosed by peri-articular thickening, and in long-standing cases the last phalanges may be bent at right angles. Effusion may take place

into the larger joints (knees), as in a case reported by Southey. The most remarkable case is one reported by Weiss: "There was effusion in the joint cavities and infiltration of connective tissues above and below the joints; once there was synovitis of the metacarpophalangeal joint of the right middle finger followed by tenosynovitis of the flexor tendons of the finger."

"On one occasion there was effusion into the knee-joint associated with exudation into the cellular tissue of the thigh and knee. . . . The skin was only reddened once, namely, in the case of effusion into the shoulder-joint; the temperature was not raised at the outset and the curve was afebrile throughout" (quoted by Barlow). The occurrence of Raynaud's disease with arthritis deformans is discussed elsewhere in this volume (McCrae).

Diagnosis.—Let me define again the main points: Raynaud's disease is an affection of the vasomotor (and trophic) centres, the anatomical basis of which has not yet been determined. The symptoms are associated with pain and vascular disturbances of the extremities—fingers, toes, hands, feet, ears, nose—local syncope, hyperæmia, asphyxia, local necrosis, usually occurring symmetrically and in recurring attacks. Sensation and motion are not involved, but in some cases there are symptoms indicative of involvements of the vascular territories of the brain (aphasia, hemiplegia), kidneys (hæmoglobinuria), and intestines (colic). The disease is most common in neuropathic individuals and women are much more frequently attacked than men. Few affections have more striking characteristics, and yet the difficulties in diagnosis are often very great.

Mild Forms.—If we could make necrosis the criterion and call no case Raynaud's disease unless the vascular changes had proceeded to gangrene, the diagnosis would be simple enough, but we cannot possibly exclude the milder forms, which escape this final stage. For years a patient may have recurring attacks of local syncope and asphyxia, with pain and great disability, but each time the cyanosis yields or disappears in an active hyperæmia. Then in an attack, it may be the tenth or twentieth, the cyanosis of one finger does not yield, necrosis occurs, and the tip of a finger or an entire phalanx is lost. Or, what is still more common, the local asphyxia persists long enough to cause a slight superficial necrosis of the pads of the fingers or of the tips of the knuckles, a bleb forms, and there is left a superficial scar. Many cases go no farther—typical cases, which never reach the stage of severe gangrene. But here arises the difficulty—where are we to draw the line in these mild forms? It is not possible—Nature draws no hard and fast lines. Thus, there are cases of chilblains with every feature of Raynaud's disease; indeed, we may say that this remarkable affection represents the typical *forme fruste* of the disease; but we very properly hesitate to group all forms of chilblains under Raynaud's disease, and yet some of the most typical and serious cases of Raynaud's disease have been preceded by ordinary chilblains, and the attacks have never come on except in the winter months, after exposure. It is the sequence of events and the periodicity that characterize the disease, not the individual elements.

Two affections with many points of similarity to Raynaud's disease, erythromelalgia and scleroderma, will be considered separately. Of many forms of local necrosis which have to be distinguished, the more important may be grouped under four headings—organic disease of the nervous system, obliterative arteritis, postfebrile necrosis, and multiple neurotic skin gangrene.

Diseases of the Nervous System.—*Syringomyelia.*—In no other organic affection of the nervous system is the condition of the fingers and toes more similar to that in Raynaud's disease, and yet in the majority of cases the added disturbances of sensation and motion make the diagnosis easy. It is more particularly in the form with sclerodactylism (Morvan's disease) that the mimicry is seen. The following differential table, modified from that of Castellino and Cardi, quoted by Cassirer, gives the essential points:

Syringomyelia.	*Raynaud's Disease.*
1. Begins gradually.	1. Begins suddenly.
2. Course very chronic; ten to fifteen years.	2. Course more acute; one to three months.
3. Begins usually in one extremity and extends slowly to the others.	3. Symmetrical onset the rule.
4. No previous vasomotor changes.	4. Vasomotor changes marked.
5. Recurring painful panaris.	5. Dry gangrene.
6. Skin cyanotic and cold.	6. Skin black and cold.
7. Dissociation of sensation.	7. Anæsthesia or paræsthesia.
8. Atrophy of muscles.	8. Atrophy very rare.
9. Ulceration common.	9. Ulceration rare.
10. Nails lost, and when reformed much curved and thick.	10. Nails dark, not deformed.
11. Necrosis and separation of bone.	11. } Atrophy of terminal phalanges
12. Fingers much curved and contracted.	12. } only.

Diseases of the Brain.—In hemiplegia the hand and foot of the paralyzed side may show marked vasomotor changes, great congestion, œdema, and occasionally necrosis of the fingers or toes. I have already referred to the cerebral complications of the disease, the transitory aphasia and hemiplegia which may accompany or precede the other manifestations, and in some of the cases in which Raynaud's disease has been said to complicate hemiplegia the peripheral and central symptoms have been due to one and the same cause. The hemiplegia of Raynaud's disease is usually transitory, and occurs in the subjects of repeated attacks of local syncope or of symmetrical gangrene. In organic hemiplegia the trophic changes leading to gangrene have rarely the same distribution as the necrosis of Raynaud's disease; the heel or the inner part of the ankle or the sole of the foot is as likely to be attacked as the toes, and there is not the same sequence of vasomotor changes.

Diseases of the Spinal Cord.—In many affections of the cord, acute and chronic, the most marked trophic changes may occur, leading to gangrene, and while the picture may resemble somewhat that of Raynaud's disease, there is rarely any difficulty in diagnosis. With chronic affections, in tabes and in tumor, trophic lesions of the toes and of the skin of the feet may occur, with a striking similarity to the lesions of the disease under consideration. Much more common is the trophic change without any vasomotor phenomena. I have seen extreme asphyxia of the feet in tabes precede the appearance of the perforating ulcer. Schlesinger has reported a case of sarcoma of the cord with symmetrical gangrene of the toes. In acute myelitis the trophic changes have rarely the features of Raynaud's disease; the toes may not be affected, but the heels or multiple patches on the legs. The gangrene comes on with much greater rapidity. I reported a remarkable case of

syphiloma of the cord with acute central myelitis and widespread trophic changes. Following trauma and in all varieties of acute compressive myelitis local gangrene may occur, but the "acute bedsore," as it is called, is a very different lesion in distribution and in appearance, and could never be confounded with Raynaud's disease.

Multiple Neuritis.—Remarkable vasomotor and trophic changes may occur in neuritis. One of the most common is the loss of control (paresis) in alcoholic neuritis, with an extraordinary cyanosis of the hands and feet. Still more remarkable changes may be seen in the acute neuritis of the infectious fevers—the hands may be swollen and cyanotic, but I have never seen necrosis. In the neuritis of the arm which sometimes follows arthritis of the shoulder-joint I have seen the whole forearm and hand swollen, painful, and red, except the finger tips, which looked livid, as though about to become necrotic. There are cases in which a multiple neuritis with motor paralysis and vasomotor changes has been associated with local gangrene. Cassirer, after a careful analysis of the literature, concludes that genuine instances are very rare. Occasionally with the polyneuritis of beriberi there is extensive gangrene. Monro reports the case of a man admitted with œdema of the legs, hyperæsthesia, loss of the tactile sensation, and absence of the knee-jerk. He had had beriberi. The tips of the toes became gangrenous, the process spread upward, and both legs had to be amputated. In the obliterative arteritis group, pain, paræsthesia, and disability may precede the gangrene and the picture may suggest a neuritis. Still more suggestive are some of the diabetes cases with anæsthesia, or paræsthesia, and a sudden onset of the gangrene. On the whole, it is not difficult to separate the vasomotor and trophic changes of neuritis from those of Raynaud's disease.

Obliterative Arteritis.—The local gangrene of this condition has many points in common with that of Raynaud's disease, and the two are often confounded. The cases, which are by no means uncommon, are met with in elderly people, in young persons who have well-marked arteriosclerosis, in syphilitic subjects, and in diabetics. Preceding the gangrene there may be attacks of the most extreme vasomotor changes. A lady, aged seventy-six years, the wife of an old friend, asked me one day to look at her right foot, which became swollen and red when she walked upon it. When at rest the feet looked alike, but after she had stood for a few minutes the affected foot became a little paler, and then, in a minute or two, got deeply cyanosed. After persisting for a few months she had a very severe attack, in which the foot became painful, the toes very dark, and it looked as if gangrene would occur, but prolonged rest restored the circulation, and with massage of the foot night and morning she escaped further trouble. No pulse could be felt in the dorsal artery of either foot, and she had well-marked senile arteriosclerosis. These are the cases which are often confounded with Raynaud's disease. They are nearly always in elderly people and are not infrequently associated with diabetes. They are very obstinate and distressing, and the pain may be atrocious. A man, aged sixty-eight years, who had had excellent health, a year before I saw him began to have pain in the right big toe and then in the right foot, which at first was pale, the doctor said definitely paler than the other. Then it began to get red and very painful at night, and from midnight to 5 or 6 A.M. he would suffer greatly. When he walked about the foot got

swollen and blue. At times he has been better, but he had spent a year of great misery. He looked a very healthy man, with good color, and his arteries were not more sclerotic than one would expect in a man of his age. The right big toe was swollen, not red; the metatarsal joint was large. The tarsus looked normal. The big toe was a little flushed, otherwise there was no difference between the feet. When he stood there was at once an extraordinary change. The right foot immediately got red, and in thirty seconds by the watch the whole foot to the ankle got congested, of a vivid red color, the veins stood out with great prominence, and the foot began to throb and ache. If he continued to walk about the toes got blue or blue-black, and on several occasions it had looked as though gangrene would follow. The most extraordinary change followed when he held the foot above the level of the body—the blood could be seen to run out of it, and in half a minute it was pale, even paler than the other, only the big toe remained of a dusky hue. Pulsation was well felt in the left, none in the right dorsal artery, and no pulsation in the posterior tibial on either side. This is a typical case of extreme vasomotor and sensory changes in connection with arterio-sclerosis.

From this stage to necrosis is an easy step, and many of these cases present the interesting combination of obliterative endarteritis, intermittent claudication, paræsthesia, and pain, with necrosis of the toes or of the whole foot. There is not often difficulty in distinguishing them from Raynaud's disease, but in a few cases in young persons the arteriosclerosis may not at first be very evident and the picture may be very suggestive. There may be marked preliminary spasm of the arteries, so that the foot looks white, and attacks of local asphyxia may come at intervals of a month or six weeks before necrosis supervenes. Barlow gives a case of a man with typical Raynaud's disease with recurring attacks which necessitated the amputation of both legs at intervals of a couple of years; the arteries showed decided thickening of all their coats.

Diabetes.—The relation of *diabetes* to Raynaud's disease is of great interest, as cases of this disease have been reported with local syncope and asphyxia. In one of Raynaud's cases the first signs of local asphyxia preceded the diabetes eight years, and it is quite possible the two diseases may co-exist. In a majority of the cases the symptoms are due to arteritis, and there is an absence of pulse in the dorsal arteries or the posterior tibials. The onset may be sudden. A man, aged sixty years, very healthy and robust, came to see me one Monday morning very much alarmed about the condition of the toes of his right foot. He had taken a long walk on Sunday, and he complained to his brother that he felt something "splashing in his right boot." To his surprise, on taking it off, his stocking was soaked with blood, which had come from a large blood blister on the outer side of the big toe. All the toes of the right foot were black, which he thought due to the staining with blood. There was no pain. The toe bled again in the night. When I saw him there was extreme cyanosis of all of the toes of the right foot, the big toe looked black, and on the other side a large bleb had burst. The toes were anæsthetic, no pulse could be felt in the dorsal artery. The urine contained a large quantity of sugar. Superficial necrosis occurred in the pad of the big toe. This was not true Raynaud's disease, but an extreme local asphyxia and necrosis in a case of obliterative endarteritis, induced directly by the prolonged exercise.

Gangrene of the Acute Infections.—This form, which is very rarely confounded with Raynaud's disease, may be due to arterial or venous thrombosis, in which case it is usually confined to one limb; or it may be associated with a very profound infection or a cachectic state, when it is often multiple. Many of these cases have been described as Raynaud's disease, but the existence of the infection and the distribution of the gangrene are sufficient for the diagnosis. The embolic and thrombotic forms involve the limbs, usually the leg and foot or the whole hand, rarely the fingers and toes alone. Pneumonia, typhus and typhoid fever, and septicæmia are the most common infections with which gangrene is associated. In some epidemics of typhoid fever it has been a more common occurrence than in the ordinary forms, and when due to a peculiarly virulent infection there may be multiple areas. The same holds true of malaria, in which the gangrene may be very widespread, as shown in the accompanying figures from a case admitted to the Johns Hopkins Hospital. There are cases in the literature which, as Barlow remarks, "are indistinguishable from Raynaud's disease, symmetrical, terminal, dry, and limited," but gangrene is an exceedingly rare complication of malaria, and the case from which the figures were taken was the only one admitted to the Johns Hopkins Hospital.

Multiple Neurotic Skin Gangrene and Pathomimia.—This is one of the rarest forms and has been variously described as *acute multiple skin gangrene, neurotic excoriations, gangrènes disséminées et successives de la peau d'origine hystèrique,* and by Dieulafoy as pathomimia. Cassirer, whose account is admirable, could only find 13 cases (1901), 10 women and 3 men, but there are many more if we include the cases of simulation. Many of the patients have been hysterical, but not all. The question of simulation has always to be considered. I saw in Paris, in Dieulafoy's clinic, a man who had this type of gangrene, which became so severe in the left arm that a surgeon amputated it in August, 1906. The spots had appeared at intervals for nine months; some of them were 5 and 6 cm. in extent. In February, 1907, the spots began to appear in the right arm—areas of gangrene which took two or three weeks to slough off and left a deep scar. Many physicians were consulted, and the case attracted widespread notice. He came to the Hôtel-Dieu in April, 1908; the "disease" had lasted two and one-half years, and he had ninety-eight scars on the arms. A few days after admission eschars began to form on the left leg just above the malleoli. Nothing could be determined as to the cause—he had not had syphilis, he was not hysterical, there was no diabetes, and nothing to suggest a special trophic lesion. The rapidity with which the eschars formed suggested simulation —one would be in full progress in an hour or an hour and a half. He confessed to having made them with caustic potash, dominated by a fixed idea which so far possessed him that he consented to have the arm amputated. Professor Dieulafoy has suggested the name *pathomimia* for this simulation of the effect of disease.[1] The cases are of interest in connection with Raynaud's disease, as a condition very similar may be produced. Anschutz has published five cases of gangrene of the big toe in military recruits, caused by carbolic acid; the toes had to be amputated. The view is gaining ground among neurologists that all of the so-called trophic hysterical lesions—the hysterical pemphigus, the hysterical ulcerations, and the hys-

[1] *Académie de Médecine*, June, 1908. Separate Brochure. *Histoire d'un Pathomime.*

terical gangrene—are simulated. In any case the form of multiple neurotic skin gangrene has little in common with Raynaud's disease, and any difficulty in the diagnosis should not often arise.

Ergotism.—In chronic poisoning with ergot a local gangrene may be caused which bears the closest possible resemblance to Raynaud's disease. The fingers and toes are chiefly affected and the gangrene is dry. Vasomotor changes with paræsthesia and sometimes contractions of the muscles may precede it. The cause is the same, namely, spasm of the arteries; but ergotism is exceedingly rare, occurs only in certain countries, and usually in endemic areas. I do not know that a gangrene similar to Raynaud's disease has ever been caused by the medicinal use of the drug.

Treatment.—The general health of the patient should be carefully studied. Sometimes it is only with the removal of some source of worry that the disease is cured. Neurasthenic and hysterical conditions must be carefully treated. In the mild forms, more particularly, the general may be more important than the local measures. When influenced by cold and damp the patient should keep the hands and feet warm, and avoid, as far as possible, getting chilled. When attacks recur in the winter only, a residence in Florida or southern California should be recommended, or if residents of Great Britain they should arrange to winter in Egypt. One of my patients, after years of suffering, had great relief in southern California.

The milder forms which do not reach the grade of necrosis are best treated by massage, electricity, and hydrotherapy. Systematic friction of the fingers and hand, morning and evening for half an hour, helps to give tone to the bloodvessels. A dead white finger may be made of a vivid pink color in a few minutes, or the cyanosis may be made to disappear quickly. There is no one measure more useful in these cases than massage if one can get it thoroughly carried out. It may be combined with hydrotherapy such as the alternate hot and cold douche to the hands or wrapping them in wet cloths for an hour or two twice a day. A general course of hydrotherapy at an institute or at one of the spas may he helpful.

Electricity may be used, and was highly recommended by Raynaud, either as galvanism or the high-frequency currents. In the severe types it is of little or no service, but in cases of paroxysmal local asphyxia and syncope it is a useful adjunct to other measures. Barlow recommends the following procedure: "Immerse the extremity of the limb, which is the subject of local asphyxia, in a large basin containing salt and tepid water; one pole of a constant current battery is placed in contact with the upper part of the limb above the level of the water, and the other pole in the basin, thus converting the salt and water into an electrode. As many elements as the patients can comfortably bear should be employed, and the current should be made and broken at frequent intervals, so as to get repeated moderate contraction of the limb. The patient should also be instructed to make voluntary movements of the digits while the galvanism is applied." In many cases a great and even insuperable difficulty in carrying out the local treatment is the pain, which is increased by the movements and by the electricity. Sometimes the radiant heat baths are most satisfactory; in one instance the pain was greatly relieved, so that the patient could sleep, and the local cyanosis was replaced by an active hyperæmia, which gradually subsided.

In the severe forms with necrosis in progress there are three indications: (1) To relieve the pain, for which local sedative applications may suffice, but very often morphine has to be given. The radiant heat may be tried. (2) To reëstablish the circulation in the asphyxiated area so as to restrict the progress of the necrosis. Massage and other local measures are impracticable on account of the pain and the presence of the gangrene. Hot douches, immersing the limb in hot water, a hot-air bath, or the radiant heat may be tried. In a case of great obstinacy and recurring attacks of gangrene of the toes and fingers Harvey Cushing suggested the use of Esmarch's bandage, so as to get the good effect of the active hyperæmia following its application. A simple tourniquet may sometimes be used. The limb is bandaged lightly and made completely anæmic; the tourniquet is then applied and kept on for a variable period. The process is usually so painful that in half a minute the patient is crying out, and the tourniquet has to be loosened. In other cases the anæmia may be maintained for a minute or two. When the limb is free the blood surges into it and causes an intense hyperæmia, which may invade the cyanosed areas of the foot or leg. Carefully practised, if the patient can stand it, this procedure gives the best results I have seen in these severe forms. It may be tried three or four times a day. The venous hyperæmia alone, by Bier's method, may be employed, but one does not get the intense active hyperæmia which follows Cushing's method. (3) Local treatment of the gangrenous part: The separation of the necrotic parts is a slow, tedious affair, and in the case of a digit may take months. Antiseptic poultices and lotions and aiding nature at times with a little surgery is as much as can be done. The parts adjacent are rarely fit for any more radical procedure. Putting the patient in a continuous warm bath for two or three weeks may be tried, particularly in cases with excessive pain. The heat also favors the separation of the slough.

Medicines are of very little service in Raynaud's disease. One would suppose that amyl nitrite and nitroglycerin would be helpful. I have seen in a paroxysm of local syncope and asphyxia the spasm gradually relax and the affected fingers grow red and hot after an inhalation of nitrite of amyl, but it is not always effective, and there are cases in which the spasm of the arterioles is not affected in the slightest degree by the drug. In the severe paroxysmal forms neither it nor the sodium nitrite appears to be of much service. For the pain opium in some form has to be used, at first locally with the other measures spoken of, and if insupportable it must be given by the mouth or hypodermically. There is great danger in the recurrent form in women of the morphine habit. I have seen three cases with this grievous complication, and it was impossible to say just how much suffering existed. In persons of middle or advanced age, with daily paroxysms of pain and cyanosis and threatened gangrene, Monro recommends opium, in pill form, in moderate doses. Antipyrin, phenacetin, and other analgesics may be tried. Ergotin has been recommended, but in cases with threatened gangrene I should say its use was contra-indicated; on the other hand, there is no more useful drug in the mild types of vasomotor ataxia in young girls—the dead hands, with puffiness, and cyanosis or redness depending on the external temperature.

CHAPTER XXVIII.

ANGIONEUROTIC ŒDEMA: QUINCKE'S DISEASE.

By WILLIAM OSLER, M.D.

Definition.—Localized swellings of the skin and subcutaneous tissues of the face and limbs, appearing spontaneously, and lasting from a few hours to a day or two. The mucous membranes of the lips, pharynx, larynx, gastro-intestinal canal, and genitals may be simultaneously involved, or they may be affected alone. The lesions in the skin are usually painless, but may be associated with itching and a sense of tension. Recurrences are the rule, and the swellings may appear at intervals throughout life. The affection may occur in many generations, and in many members of a family. In the majority of cases it is not serious, but the gastro-intestinal form causes severe colic, and in a few instances death has been caused by œdema of the glottis. The affection is closely related to urticaria.

History.—A disease with such marked peculiarities is not likely to have escaped the notice of the older observers, and Joseph states that cases were reported in 1778 by Stolpertus and by Erichton in 1801. Graves gave an excellent description in 1848, and Milton[1] reported cases under the excellent name of giant urticaria, but general attention was not called to the disease until the description by Quincke in 1882,[2] since which date there have been scores of communications on the subject. The literature is fully given in the *Index Catalogue of the Surgeon-General's Library*, 2d series, vol. xii, and in Cassirer's monograph.[3]

Nomenclature.—The name here adopted is the one in general use by English and American writers. Others are: Giant urticaria (Milton); urticaria œdematosa, urticaria tuberosa, wandering œdema; intermittent œdema, acute recurrent œdema; œdème rheumatismal essential; œdème rheumatismal à répétitions; and hydrops hypostrophos (Schlesinger). The nodosités cutanées éphémères of Févérol, as I read his description, belong to the rheumatic subcutaneous nodules.

Etiology.—The disease is not uncommon. The writer has notes of 18 cases in private practice. There were 16 cases at the Johns Hopkins Hospital in a period of nearly twenty years among 23,000 medical cases. It is more frequent among the better classes. In my series women were much more frequently attacked—14 to 4. In the cases collected from the literature by Cassirer there were 70 men and 63 women. A majority of the cases are in persons under twenty years of age, but it may occur at any period. J. P. Crozer Griffith reports cases at one and one-half months, and the grandfather of one of my patients who had suffered from boyhood had occasional attacks

[1] *Edinburgh Medical Journal*, 1876.
[2] *Monatsheft. f. prakt. Dermatologie*, 1882.
[3] *Die Vasomotor-trophischen Neurosen*, Berlin, 1901.

after his ninetieth year. With advancing age the tendency to attacks lessens. In one man the attacks began after his fortieth year.

In a majority of the cases no exciting cause can be discovered. Unlike ordinary urticaria, digestive disturbances and errors in diet play a very small part. One of the writer's patients thought that the eating of fish was sometimes the cause of an attack. In one case strawberries and coffee would at once bring out the œdema, a peculiarity which had persisted for twenty-two years. On the other hand, some of the most obstinate cases are entirely uninfluenced by diet.

Nervous Influences.—This appears to be the most important factor. In the first patient I saw with the disease, a young dentist, who had recurring attacks in the eyelid and forehead, worry, overwork, or any depressing influence was liable to bring on the œdema. A nurse, subject to the malady, had at times to give up a patient, who caused her much anxiety, on account of the recurring attacks.

Infections.—Rheumatic pains, swelling of the joints, tonsillitis, and, in a few cases, definite rheumatic fever have accompanied the outbreaks. Giant urticaria may occur alone or with other skin manifestations. In children there may be fever, with constitutional disturbances, pains in the joints, severe colic, vomiting, and polymorphous skin rashes; in one attack, purpura; in a second, ordinary urticaria; in a third, angioneurotic œdema; in a fourth, colic alone. In my series of 28 cases, reported under the title (for want of a better) "The Visceral Lesions of the Erythema Group," there were several cases of this character.

Malaria has appeared to be a factor in a few cases (Matas). The intoxications have played no role in my series. Alcohol has been mentioned by a number of observers. In a man, aged forty-four years, addicted to morphine for many years, and believed to be cured, though he was taking three grains a day, œdema of the legs came on without any obvious cause, and had persisted for nearly three years. There was no albumin in the urine and no corpuscular anæmia—only the ashen pallor of the morphine *habitué*. The œdema had given him great trouble, and had been the cause of much discussion among his physicians. It came on while he was taking as much as twenty-five grains of morphine a day, and he thought that it had diminished within the past years when he had reduced the quantity to about five grains daily.

Of the endogenous poisons the result of perverted metabolism—anywhere from the moment the morsel of food is rolled round the tongue until its constituents have been through the furnaces and are cast out as ashes and smoke—we talk a great deal, but we know nothing, so far, at least, as this disease is concerned. In organic affections of the nervous system œdema is not uncommon, but the cases scarcely come in this category. In poliomyelitis anterior, in compression paraplegia, in peripheral neuritis, in monoplegias, œdema may occur, but the whole limb is, as a rule, involved, and it has not the transitory character of the form under consideration. In the neuritis of typhoid fever or of arsenical poisoning the œdema may be very localized. But in none of these conditions is the œdema exactly like the Quincke form—it is more permanent and often more extensive, and the same may be said of the posthemiplegic œdema. In rare cases œdema may occur in the region affected with the lightning pains of locomotor ataxia.

As already mentioned, emotional disturbances are very apt to bring on

an attack, and some of the most obstinate cases are in neurasthenic subjects. At least one-half of the cases in my series belong to this type. One patient who described herself as "a bundle of nerves," and with "pain wherever I have a nerve," had had œdema for more than twenty years, scarcely ever passing a week without an outbreak. When I saw her the back of the left hand, the ulnar side of the right hand, and the skin over the left elbow were affected. The ears often became stiff, swollen, and red. She had had colic, and as a younger woman was subject to "bruises"—blue spots which came out spontaneously. The irregular distribution of the swellings in these neurasthenic patients separates the condition clearly from the hysterical variety.

Many of the patients have had other nervous affections—migraine, neuralgia, and exophthalmic goitre. In the last-named disease, erythema, urticaria, spontaneous and factitious, are common, but very rarely giant urticaria; a persistent œdema of the legs may occur which may have the tense, indurated aspect of scleroderma. In the psychoses, angioneurotic œdema is occasionally met with. The patients are very apt to be depressed and a settled melancholy may ensue. The first case I saw, the young dentist already referred to, committed suicide.

Menstrual disturbances may be associated with transitory œdema. As is well known, at each period there may be puffiness of the hands or of the face. In at least six of my cases the attacks were more likely to occur at this time, and in individuals strongly predisposed, or with the hereditary bias, the association is common. At the climacteric, vasomotor disturbances are frequent, and occasionally the waking numbness and the acroparæsthesia are accompanied by swelling of the hands and feet and puffiness of the face.

In susceptible individuals a slight trauma may suffice to bring on an attack. Cold, which is an important factor in certain cases of ordinary urticaria, does not seem to play any part in angioneurotic œdema. In a few cases only the uncovered parts—face and hands—have been affected. In very sensitive subjects, placing the hands in cold water, a cold breeze on the face, or exposing the buttocks in a cold water-closet, have sufficed to bring on a local attack. In none of my patients did the season make any special difference.

Heredity.—Heredity plays a very important role in the disease, and the cases in this category are of unusual severity. Quincke, Dinkelacker, Strubing, and others have reported families in which it has occurred. In the family I have described,[1] the table of which is given on page 651 (hereditary angioneurotic œdema), the disease occurred through five generations and affected more than twenty people, causing at least two deaths. I have since seen incidentally two other members of this family, both with very severe forms of the disease. The serious nature of the trouble may be gathered from the following account: Mrs. W., aged fifty-four years, is of the fifth generation of the family. Her mother had attacks, and also one sister; one brother is well and strong. She has had three children, two sons and one daughter, none of whom has had attacks. The angioneurotic œdema began in her twenty-seventh year, after the birth of her second child, with colic and swelling of the skin of the abdomen. Then the arms and legs

[1] *American Journal of the Medical Sciences*, 1888, xcv, 362.

began to swell at times, but never very badly. Seven years ago the face was affected, the eyes closed, the throat was swollen, and the breathing obstructed, so that the wheezing could be heard all over the house. From this time her life has been one of great misery from the frequent recurrence of the attacks in the face, arms, legs, and chest, and occasionally in the throat. In August, 1904, with an attack in the face and throat, she had colic and vomited blood. The swellings are usually white, sometimes a little red. In the severe attacks there is fever. The duration is from ten to thirty-six hours. The recovery is very rapid. Strawberries or coffee will at once cause an attack. Fatigue or emotional disturbance is sure to be followed by a swelling. When I saw her she had a large infiltrated œdema, with redness of the region of the right elbow and well-marked lines of demarcation. On the left arm there was a white swelling on the inner aspect of the elbow and two black and blue spots from an attack a few days before on the outer surface of the left arm. The severe attacks are always accompanied by erythema, and she has at times large ecchymoses, but never the ordinary wheals. The neck has swollen so as to obliterate the outlines of the chin.

GENEALOGICAL TABLE SHOWING ANGIONEUROTIC ŒDEMA IN THE FAMILY OF T.

I.	II.	III.	IV.	V.
Margaret,[1] b. 1762, d. 1834.	Samuel,	3 children all affected; 1 (John) died of it.	One girl affected.	
	Stacy,		*Hamilton*,	*Thomas*, *Lizzie*.
			Rebecca, died of it.	2 children, aged 17 and 11, one of whom has recently had her first attack.
	Allan, 10 children, 3 affected,	*George*,	Almira, *Mary*, *Julia*, *Katie*, *Edward*, *Maggie*, *George*.	
		Emma, single.		
		Sallie, married; no children.		
	John M.	4 children; 1 (Angey) affected.		

[1] Those in italics have suffered with the disease.

In the other member of this family, in the sixth generation, attacks of colic occurred for years before any local skin swellings made the diagnosis clear. Meanwhile, she had had her appendix removed, as the recurring abdominal attacks were believed to be due to appendicular colic. The severity of the hereditary form is illustrated by the cases of Griffith;[1] both father and daughter died of the acute œdema of the larynx.

I do not think any of the families have been studied with sufficient care to get details as to the frequency of transmission through the mother or the father on the value of Mendel's law. In the family reported by me it was impossible to get accurate details, as the members had scattered far and wide, and one of those just referred to did not know of the existence of a peculiar disease in her family.

Hysteria.—Sydenham first recognized an œdema associated with hysteria. Charcot and his pupils made it the subject of several important studies. The common variety bears very little resemblance to the ordinary angio-neurotic œdema, except that in both there is infiltration of the subcutaneous tissue. The affection is usually superimposed on some well-marked hysterical manifestation—a paralysis or a contracture. It is not paroxysmal or transitory, but persists often for as long as eighteen months or two years, and, as a rule, is accompanied by disturbances of sensation. The areas affected usually correspond with the natural divisions of the body, an arm, a leg, a mamma, *i. e.*, they are "geometrical" or "segmental," or conform to areas covered by articles of clothing, stocking, sock, or glove. The ordinary type of Quincke's œdema may occur in hysterical subjects, and many cases of the kind are reported; but the association is not so common as with neurasthenia. In not one of my cases did hysteria co-exist. Edgeworth has reported a series of cases[2] in which transitory œdema of a segmental destribution occurred in young subjects, and in three of the seven cases there were disturbances of sensation suggestive of hysteria. In one instance the duration of the attacks ranged from two days to thirteen weeks.

Pathology and Relation to Other Affections.—Is Quincke's œdema a disease *sui generis* or is it only a symptom complex with relations more or less close with other affections and a varied etiology? It is not easy to determine. An affection which "breeds true" through six generations and presents in each identical features seems worthy of special designation. But the œdema itself is only a symptom, behind which is the effective cause for which we have so far no clue. Œdema, like arthritis, is caused by a number of different agents, and as in many forms of arthritis we have to be content with anatomical and clinical features, so in this special variety of œdema it may be urged that even in the absence of a definite etiological factor the clinical features and the remarkable heredity suffice to raise it to the dignity of a disease. The chief difficulty arises when we consider its close relations. The special lesion is nothing but a wheal of urticaria "writ large." The difference is one of degree and amount of exudation, not of kind. The erythema of an ordinary wheal is often present, and while the plasma plus leukocytes forms the chief part of the effusion, red blood corpuscles do pass out of the vessels and a staining may be left.

[1] *British Medical Journal*, 1902, i, 1470.
[2] *Quarterly Journal of Medicine*, 1909, ii, 135.

Milton's phrase, "giant urticaria," was most happily chosen. Ordinary urticaria has its visceral manifestations, and there are cases which Doctor A. will diagnose Quincke's œdema in this attack, and Doctor B. simple urticaria in the next outbreak, and both may be right.

Another interesting relationship is with purpura—which has an identical lesion—an exudate of blood, with a qualitative difference, the red blood corpuscles being in excess, and, as a rule, there is not serum enough to raise a wheal; but in every spot of purpura the three elements of the blood are poured out. Gastro-intestinal crises are common in certain forms of purpura, and as in angioneurotic œdema, they may antedate for months the cutaneous features, or may occur quite independently of them. It is additionally difficult to label Quincke's œdema as a special disease when we consider that in the same subject at different periods the skin lesions vary. In papers in the *American Journal of the Medical Sciences*[1] I have reported a series of cases, 28 in number, illustrating the visceral complications of a group of skin lesions characterized by erythema, purpura, urticaria, and œdema. In individual cases followed for a number of years, with the gastro-intestinal crises, various lesions occurred, so that in one attack the disease could be called Henoch's purpura, in another a multiform erythema, in a third simple purpura, in a fourth angioneurotic œdema. Certain cases of Quincke's œdema present this variability, and even in the hereditary form, as illustrated by the patient referred to on p. 650, the lesions may be those of a diffuse erythema, with exudation. The skin lesions are too unstable to be of value except for a most superficial classification, and the visceral manifestations are practically the same in the whole series. Indeed, there are cases of hæmophilia which clinically come in this category. I have seen spontaneous ecchymoses, purpura, and intense colic so severe that appendicitis was suspected in a well-known "bleeder." In the absence of fuller knowledge we are really in a quandary, and have to be content with a clinical classification of the cases. An attempt to group them etiologically is very unsatisfactory, as we really know so little about the true causes, and there are few departments in which speculation is so easy and at the same time so useless.

There are four conditions in which exudative skin lesions (erythema, purpura, urticaria, œdema) are met with in connection with gastro-intestinal crises and sometimes more serious internal complications, as acute nephritis.

I. **Acute Infections.**—The clinical picture of Henoch's purpura or of Schönlein's disease or of an acute exudative erythema may be met with in rheumatic children, sometimes with arthritis, endocarditis or pericarditis, and there may be fever and the general features of an acute infection. The skin lesions may be associated with some other infection, as gonorrhœa, or with a local ulceration.

II. **External Poisons.**—A large group of substances, animal, vegetable, and mineral, possess the power of causing exudative skin lesions. All are sensitive and react to certain of these, but in a majority of cases it is not a general but a special condition of the recipient, a sensitiveness, an idiosyncrasy, as we say. Quinine will cause an erythema, iodide of potassium

[1] 1895, cx, 629, and 1904, cxxvii, 1; *British Journal of Dermatology*, 1900, xii, 227; and Jacobi *Festschrift*, New York, 1900.

a purpura, strawberries, urticaria, shell-fish a local œdema, and the capability thus to react to certain substances may be inherited or "run" in a family.

III. **Endogenous Poisons.**—In diseases characterized by profound disturbances of metabolism exudative skin lesions are rare. In gout and diabetes the types of auto-intoxications, these complications are not often seen; they are more common in chronic Bright's disease. There is more evidence in favor of hepatic poisons—the oft-recurring urticaria in some cases of gallstones (even without icterus), and the frequency of purpuric and allied skin rashes in jaundice. The cases in children with recurring colic and gastro-intestinal disturbance associated with outbreaks of purpura or purpuric urticaria suggest an auto-intoxication, but we have no positive data, not a clue as to the nature of the poison or the locality of its formation.

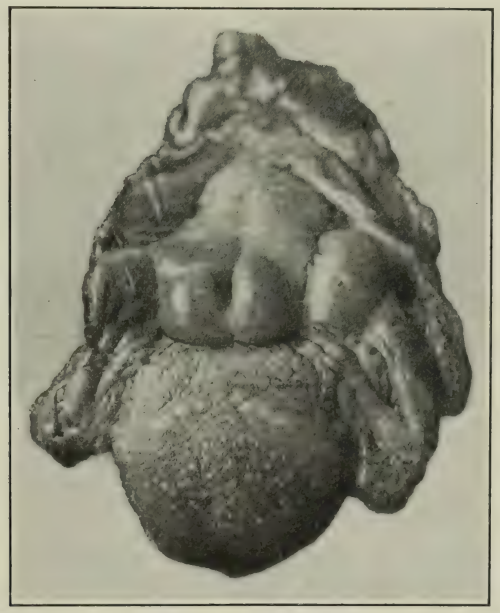
IV. **Heredity.**—Certain persons are born with a special susceptibility to exudative skin lesions. There are families all the members of which present these reactions to particular substances; there are families some members of which are liable to attacks of local œdema, a peculiarity which has been traced through six generations; and lastly, there is an hereditary œdema of the legs (Milroy's disease) which has probably nothing to do with the forms under consideration. These are the main facts in connection with heredity and exudative affections of the skin and mucous membranes. There are all sorts of difficulties in the way of any satisfactory explanation of the remarkable phenomenon of localized œdema occurring in several generations. It is not like a chemical anomaly, as cystinuria or alcaptonuria—the susceptibility is only in certain individuals, and may be delayed until the forty-seventh year; it may occur early in life and then disappear, or it may last to an advanced old age. The inconstancy, the irregularity, is the most striking feature, both in distribution and in the incidence of attacks in affected families.

If we understood the pathology of an urticarial wheal we might discuss intelligently these remarkable varieties of local œdema. Gilchrist has shown us how easily the anatomy of a wheal may be studied in factitious urticaria. Here a direct irritant, a scratch, is followed by a vasomotor hyperæmic reaction, a perfectly normal phenomenon on a healthy skin; but in a sensitive person along the line of the irritation something else has happened; the capillary walls have been made permeable, and an exudate of all the elements of blood, but chiefly of the serum, forms the wheal. We have no idea why the same sort of scratch will in A cause hyperæmia, in B anæmia, and in C factitious urticaria. The vascular change is a vasomotor phenomenon—vasodilator or vasoconstrictor—but what is the change which permits of the exudate? Is it neurotic, an alteration under nervous influences of the rate at which the vascular cells secrete the fluid, or is it a physical change under the influence of the irritation, which permits a more rapid osmosis through the capillary membranes? If we could answer these questions for simple factitious urticaria we might approach the problems of the other exudative lesions in a hopeful mood. In the case of Quincke's œdema we have to suppose in certain areas a vulnerability of the capillary walls which permits of an exudate at so rapid a rate that the efferent channels cannot deal with it, and in consequence the lymph spaces are distended and the skin swells. Why this should occur in the lip to-day,

in the gastric or intestinal mucosa next week, and on the hand next month—why it should come on in a perfectly healthy person and recur at intervals for a year or two and disappear completely, or why the liability should occur in families but only in certain members, and be transmitted for six generations—these are questions for which we have as yet no answer.

Symptoms.—There are three groups of cases, mild, moderate, and severe. A young woman who has been overworked or has had worries awakens one morning with a sense of itching over the forehead, and on looking in the glass is surprised to find one eyelid swollen and the side of the face and forehead puffy. By noon the swelling has gone. The lip may be œdematous, or there is a puffy swelling of the back of one hand, or a local infiltration the size of a saucer on the skin of one leg. The attacks

FIG. 11



The larynx and neighboring tissues in angioneurotic œdema.

recur at intervals for five or six months, or for a year or two, and then disappear. The œdema may always recur in the one place—the eyelid, a finger, or the back of one hand. The general health is not disturbed, and the outlook for complete recovery is good.

In a second group of cases the manifestations are more severe, and the disease lasts for a much longer period, even for a lifetime. The swellings are more voluminous, and troublesome by bulk alone. The hand may be like a boxing glove; the under lip may be so swollen that it is difficult to feed the patient; both eyes may be closed, the neck may be obliterated, both feet may be enormously swollen, or the penis may be so infiltrated as to impede micturition. In these forms the mucous membranes may be affected and the hemorrhagic œdema of the walls of the stomach may cause

colic and vomiting, or in the intestines severe cramps or crises with diarrhœa. The mucous membrane of the mouth and throat may be involved, and in these cases the skin lesion is not always a simple œdema, but there may be erythema, with hemorrhages. The frequent recurrences of these manifestations may render the patient's life a burden. The attacks may begin in childhood, and persist even to advanced old age, or they may not start until adult life, and then only persist for a few years.

In a third group of cases the localization of the œdema in the throat and larynx threatens life with each attack, and there are now in the literature half a dozen or more fatal cases. The case reported by Roger Morris[1] illustrates the serious character of some of these cases. A man, aged twenty-one years, had had repeated attacks of swelling of his feet and hands. Then he began to have the larynx affected, and twice tracheotomy had to be performed. In the fatal attack he was found sitting up in bed, with urgent dyspnœa, and before the doctor could reach the house he was dead. The illustration, Fig. 11, gives, for the first time, I believe, a picture of the extent of this form of sudden œdema of the glottis.

Character of the Skin Swellings.—As a rule, it is a simple œdema without erythema—an infiltration of the subcutaneous tissues and of the skin itself. The appearance depends in the degree of laxity of the tissues—the eyelid and the lip are the two types. In the former there is a gelatinous œdema, soft and puffy, which pits deeply, and which has a bluish white tint. In the lip the swelling is firmer, may not pit at all, and has an opaque-white aspect. The skin is usually anæmic and smooth; when the œdema is persistent, blebs may form. The appearance varies greatly with the stage—at the height of the exudation the areas are tense and opaque-white, contrasting sharply with the surrounding skin; as the swelling subsides the skin becomes relaxed, and even flabby and wrinkled.

The size and extent of the swellings vary greatly and both hands may be as big as light-weight boxing gloves. There may be areas of infiltration as big as saucers or the size of a soup plate on the trunk or thigh; the under lip and chin may be so swollen as to render the features unrecognizable and make eating and even breathing very difficult; or the outlines of the neck may be obliterated. In mild cases small areas, 2 to 5 cm. in extent, are present, or the back of the hand, one finger, or an eyelid swells, or there are half a dozen large wheals on the trunk. In all varieties the outlines are usually well defined, and in the case of the swelling of the hand, there may be a ridge of the wrist an inch or more in height.

The color is not always opaque-white, but may be translucent or waxen, sometimes with a slight yellow tint. Erythema may be present even in large areas of œdema, as in the hereditary case already mentioned; and so marked may this be as to give an appearance of an acute inflammatory œdema. A transient efflorescence may be seen in an acute swelling of the lip or of the penis. In the smaller areas, which resemble rather large wheals of ordinary urticaria, there may be a zone of erythema. In regions were the skin is very loose, eyelids and prepuce for example, blebs may form.

The temperature is not raised; indeed, in the large areas with a deep œdema and much anæmia it may be 6° or 10° below the skin of the corre-

[1] *American Journal of the Medical Sciences*, 1905, cxxx, 382.

sponding part. In the form with erythema there may at first be an increase in the temperature, readily perceptible to the touch. In a case of Starr's, in which the œdema of the hand followed immersion in cold water, the temperature rose more than 20° in fifteen minutes.

Subjective Sensations.—Subjective sensations may be absent altogether. One of my patients could not tell whether the forehead was swollen until she looked in the glass. She could tell immediately on waking whether the eyelids or the lower face were swollen by the stiffness and restraint in motion. Prickling sensations, a sense of burning, heat, and itching are common, but intense itching, such as is so distressing in ordinary urticaria, is very rare.

Regions Affected.—The face and extremities are the common situations. Among 71 cases, in 29 the first swelling was in the face, in 22 in the extremities (Collins). The irregular asymmetrical distribution is very characteristic of this type—an eyelid, one hand, the side of the thigh, the dorsum of a foot, the chin, one finger. In one of my patients, in whom the swelling was usually in the hand, as a rule both were affected, but sometimes only one. The segmental distribution is not common, but, as Edgeworth has pointed out, it may occur in Quincke's œdema and be quite as marked a feature as in the chronic hysterical form. There are cases in which the swelling is always in the same place, usually the eyelid, a form to which ophthalmic surgeons have given special attention. A peri-articular variety has been described, and Rendu has reported the sudden onset of supraclavicular swellings resembling those of angioneurotic œdema. The intermittent hydro-arthrosis and the intermittent parotid swelling scarcely come in this category, although Schlesinger regards them both as closely related affections.

Mucous Membranes.—One-half the cases in my series had involvement of the mucous membranes. By far the most common is swelling of the inner aspect of the lips and cheek, either alone or with the tongue. This may be in connection with a local œdema of the face, or in a person subject to attacks the mouth may be affected alone. The swelling may be diffuse or very localized. I have seen the very tip of the tongue involved. Very serious are the attacks in which the whole mouth, with the sublingual tissues and subcutaneous structures of the neck, is involved. The cavity of the mouth may be almost closed, and for some hours it may be impossible to take food or drink. The throat may be the seat of a local œdema confined to the uvula and the arches of the palate. The uvula may be as big as the thumb. The tonsils are rarely involved.

Respiratory Passages.—Much more serious is the œdema of the respiratory passages. The nose is not often affected. I have seen the external orifices nearly closed, and the mucosa involved with the skin. Isolated swellings of the turbinated bones or attacks like hay asthma are of rare occurrence. Bloodgood has described a case which he called angioneurotic œdema of both accessory sinuses and of the cheeks. The condition persisted for months. The sinuses were opened and a condition of intense œdema of the mucous membrane was found.

Œdema of the larynx is a rare event. It does not often occur alone, but usually in association with swelling of the pharynx or with some external manifestation. The onset is sudden, very often in the night, and the patient wakens with dyspnœa and a feeling of heat and irritation in the

throat. The condition may become rapidly worse and death may occur before help arrives. In Roger Morris' case, already referred to and the illustration of which is given, the man's life had twice been saved by tracheotomy, and in the third attack the doctor arrived too late. In Griffith's cases father and daughter died of œdema of the larynx. One case, and possibly two, in the family I reported died with this complication. T. H. Halsted[1] has discussed fully these complications in the upper air passages. It has been suggested that certain forms of asthma belong to this disease, but I do not think this is very likely. None of my patients had asthmatic attacks, and I do not see any cases in the literature in which asthma alternated with well-marked skin lesions of the pure angioneurotic œdema type. On the other hand, the association of asthma with ordinary urticaria is well known, and I have seen one case in which, in repeated attacks, a crop of urticaria came out, with intolerable itching, over the spine in the region of the third and fourth dorsal vertebræ.

Conjunctiva.—The conjunctiva is rarely affected alone, but in the cases of œdema of the lids it is not uncommon to see the mucous membrane greatly swollen. Cases are reported with chemosis and little or no involvement of the skin.

The Gastro-intestinal Canal.—This is involved in about 34 per cent. of the cases (Collins); ten of my patients had attacks of colic. We know now the nature of the local trouble, as exploratory operations have confirmed the view that it was an œdema of the wall of the bowel, and in a case reported by Morris, in washing out the stomach to relieve the severe vomiting, a portion of the mucosa was removed, and on examination was found to be in a state of acute œdema.

Colic is the common abdominal symptom, coming on suddenly, and often reaching an extreme grade. As a rule, it occurs with the skin manifestations, but it may be the only feature, and there may be no clue to the nature of the trouble. In a majority of cases it is a "dry colic," the pain central, more or less continuous, with paroxysms of greater intensity. The patient may roll about in the bed or be doubled up in an agony of pain. The abdominal walls are tense, there is not often tympanites, and there may be no local tenderness. Appendicitis, gallstone colic, or renal colic is suspected, and in a considerable number of cases laparotomy has been performed.[2] There are many instances in which the abdominal symptoms have preceded for months the onset of any skin lesions. In severer attacks with the colic there is vomiting coming on with the pain and lasting for many hours. The patient may look very ill, with pallor, small pulse, and features of collapse; and at the end of ten or twelve hours the symptoms may all disappear, and an outbreak of local œdema gives the diagnosis. The gastric crises may be the most troublesome feature of the disease, and may recur after the attacks of œdema of the skin have ceased.

With the gastric symptoms and colic there may be intestinal symptoms, diarrhœa, meteorism, and even the passage of blood. In my experience these have not been so common in the cases of pure angioneurotic œdema as in the group of closely allied cases known as Henoch's purpura. The abdomen may be swollen and tender, and the picture—sudden onset, vomiting,

[1] *American Journal of the Medical Sciences*, 1905, cxxx, 863.
[2] Osler, *Ibid.*, 1904, cxxvii, 751.

pain, diarrhœa, pallor, with feeble pulse—may suggest perforation of a gastric or a duodenal ulcer. The passage of blood in children may suggest intussusception. In no case in my series of angioneurotic œdema was there melæna.

Renal Symptoms.—Renal symptoms are not common. Albuminuria has been met with, and in a case of Oppenheim's the state of the urine suggested an acute nephritis. Paroxysmal hæmoglobinuria occurred in a case of Joseph's. When the abdominal pain is lateral or starts toward the pubes, renal colic may be suspected.

Cerebral Symptoms.—Cerebral symptoms have been reported, particularly in connection with the family form—headache, somnolence, vertigo, and marked depression.

Fever rarely occurs, but after a severe gastric crisis there may be a slight elevation of temperature, and for a day or two the tongue is furred and there is loss of appetite. It is surprising with what rapidity recovery may take place, and within twenty-four hours after the most alarming symptoms I have heard a patient ask for solid food and have an appetite for a good meal.

Diagnosis.—Quincke's œdema is easily recognized—it is localized, white, transitory, and recurrent. Only in the few cases, such as those reported by Edgeworth, when it is segmental and in the legs, could any difficulty arise. Ordinary intelligence is required to distinguish the various œdemas of stasis and of cachexia. The hysterical form is more chronic and has the characters already given. Milroy's œdema is confined to the legs and is hereditary. In a large majority of cases the lesions are the same in different attacks, and there is a predilection for the same locality; but in children and in young adults the lesions are polymorphic, and the case may be a typical angioneurotic œdema to-day, but next week there is a severe attack of hives, or an outbreak of purpura, or a peri-articular region is erythematous and infiltrated. Severe recurrent generalized hives may have many of the features of Quincke's disease. A girl, aged twenty-two years, had from her fifth year every three or four months attacks characterized by nausea, vomiting, a constricted feeling in the chest, and an outbreak of urticaria of the most extraordinary character. The face was uniformly swollen, the eyes closed, the hands and feet greatly swollen, the skin of the body thickly set with hives. The mouth and throat were also swollen. In her twenty-first year she was almost free. I saw her recovering from an attack in which the face alone was attacked and the swelling had very little redness. Diet had nothing to do with causing the outbreaks.

It is not always easy to distinguish from the swelling of a local thrombosis, particularly the recurring form in young persons which Briggs described from my clinic. In a young chlorotic girl with multiple cutaneous swellings on the skin of the trunk the diagnosis of angioneurotic œdema was suggested, but there were thrombi in the veins of the legs. Where the thrombus is deep and the swelling very localized, as in the calf of the leg, the difficulty may be very great. I saw such a case with Dr. Ruffer, of Washington, in an exceedingly neurotic young man. It is rarely a white œdema, and it is much more persistent than the ordinary giant urticaria.

In one case the preliminary œdema of scleroderma was mistaken for Quincke's disease, but it was permanent and the hardening and change in color of the skin were soon apparent.

As a rule, with the skin lesions well defined, there is no difficulty in recognizing the cases, but it is a very different matter when the gastro-intestinal symptoms are dominant. I have reported cases in which for years colic antedated the skin lesions, in others the rashes are of so trifling a nature that no account is taken of them. Appendicitis is naturally suspected. The pain, as a rule, is much more severe, and the patient writhes about in the bed in a manner very unusual in appendicitis; local tenderness is rarely met with in the right iliac fossa; there is no fever, and lastly the attack is over in a few hours, from three to six or eight. In severe cases there are vomiting and diarrhœa and sometimes blood is passed per rectum. There are cases in which these attacks recur with great frequency, once a week or once in ten days, and in the absence of any skin manifestations it may be very hard to reach a diagnosis. A number of patients have been operated upon, either for appendicitis or for intussusception. In one case stone in the kidney was suspected, as the colic was always in the flank. One patient was operated upon for gallstones and afterward for appendicitis.

The most serious internal complication, œdema of the larynx, is easily recognized, as it rarely occurs alone, but commonly in association with swelling of the lips or face. Mild grades of obstruction usually occur before a serious attack, but as in the case mentioned there may be very little warning. The features of acute obstruction are only too evident, and tracheotomy or intubation may be necessary to save life.

Prognosis.—The attacks usually recur—this is the rule. Many patients after having the disease for eighteen months to two years get quite well. The duration in my series ranged from eighteen months to a life of exceptional duration. The younger the patient the better the prognosis. The family form seems peculiarly obstinate, and may persist to advanced age. When diet has a marked influence on bringing on attacks the outlook is good. The disease is only occasionally dangerous to life, and that always through the œdema of the glottis.

Treatment.—The general condition must be carefully studied. Many of the patients are neurotic, and a suitable course of hydrotherapy, massage, and electricity may be given. An outdoor life is an important element in the cure. In young persons the outlook is usually good, particularly in children in whom the œdema is associated with colic, etc. Several patients in my series have now been quite free from attacks for eight or ten years. The angioneurotic œdema of the face, particularly of the eyelids in young persons, is singularly obstinate, and may resist all forms of treatment.

Careful inquiry should be made as to the influence of diet, and, as a rule, some change should be made or certain articles cut off. Coffee or tea may be the offending substance, or the patient may be eating too much meat. One patient in whom the attacks were very frequent was benefited by a milk diet. In strong, full-blooded persons the use of laxatives may be helpful. I tried a salt-free diet with one patient without any success. On the whole, my experience has been against any special influence of diet in the disease. In this respect it resembles certain forms of protracted urticaria, as in the young girl whose case is mentioned under diagnosis. She had been "dieted" by nearly every physician of distinction in Europe and the United States, and she had had all the cures, without the slightest help.

In children some of the very protracted forms seem to be associated with gastro-intestinal trouble, which should be carefully treated. Many cases

have been dealt with on the view of intestinal intoxication. In a woman with great flatulency, irrigation of the large bowel was helpful. Many medicines have been recommended, strychnine, the bromides, alkalies, the salicylates, antipyrine, ergot, belladonna, etc.; and in the chronic cases it is only natural that all sorts of drugs should be tried. I have only found two of service: nitroglycerin or the nitrites, given in ascending doses until effects are felt, *i. e.*, until the patient feels the flushing and the headache. It is useless to order simply one or two minims of a freshly made 1 per cent. solution of nitroglycerin. The dose must be gauged to the individual, who should be told to increase it gradually until he feels the effects, and then let him continue the treatment for periods of ten days, with intervals of five days. The other drug is calcium, recommended by Wright. In this group of cases I have given it a thorough trial, and in two out of five cases it seemed most helpful. In Case 18, a young man who had had very severe attacks, and had been under treatment for eighteen months, was rapidly relieved, and although he had a few recurrences he has now been a year without any œdema. He took calcium lactate, 20 grains (gm. 1.3) three times a day.

In children with attacks of colic and periodic outbreaks, gray powder, given for a week or ten days at a time, has seemed helpful.

The gastric and intestinal crises require prompt treatment—a hypodermic of morphine gives immediate relief; but it is well to be careful in the hereditary and recurrent forms, and, if possible, use strong carminative and local applications.

In a case with recurring attacks of œdema of the larynx, an intubation apparatus should be in the house, and some one should be taught its use in case of emergency.

HEREDITARY ŒDEMA OF THE LEGS (MILROY'S DISEASE).

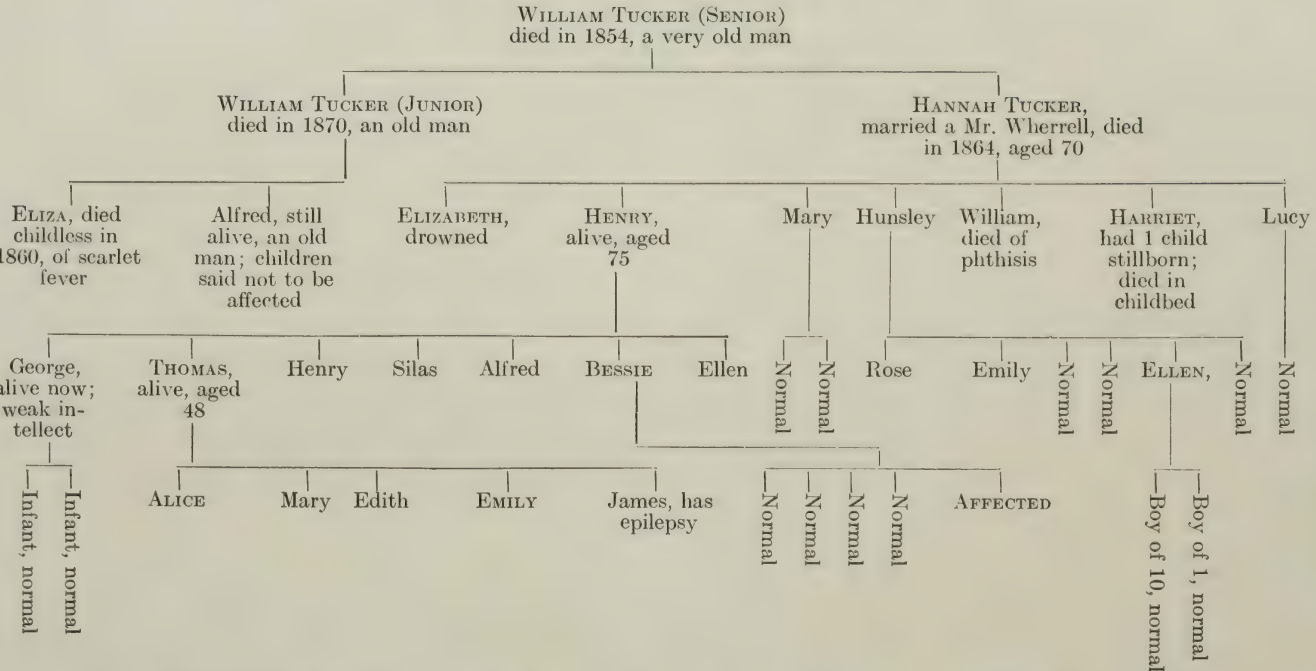
In 1892 W. F. Milroy, of Omaha, reported, under the name of "An Undescribed Variety of Hereditary Œdema,"[1] a remarkable series of cases, characterized by persistent œdema of the legs. The disease affected 22 individuals among 97 persons in six generations. Dr. Milroy wrote to me about the cases, which I at once recognized as peculiar, and, so far as I could ascertain, undescribed. A note in the condition was made in my text-book under angioneurotic œdema. Meige, in 1898, described eight cases in four generations,[2] and a good many cases have been reported in France. In 1902 Rolleston[3] reported 3 cases in two generations, and in 1908 Hope and French[4] described a remarkable family in which 13 members were affected out of 42 persons, traced through five generations.

The following are the important features:

Heredity.—The genealogical table of the Tucker family, described by Hope and French, and reproduced on page 662, gives a good idea of the persistence of the affection through five generations.

[1] *New York Medical Journal*, 1892, lvi.
[2] *Presse Médicale*, 1898.
[3] *Lancet*, 1902, ii.
[4] *Quarterly Journal of Medicine*, 1908, i.

Genealogical Table of the Tucker Family.



The individuals whose names are printed in small capitals had, or have, the family complaint of "swollen legs," mostly with "acute attacks" as well.

PLATE XVIII





Symmetrical Gangrene in Malarial Fever.

PLATE XIX





Hereditary Œdema of the Legs. (Milroy's Disease.)

From the *Quarterly Journal of Medicine.*

The percentage of persons affected varies from only 2 or 3 in certain families to nearly 20 per cent. among 97 persons in Milroy's family. Males and females are about equally affected, and we have no explanation of why one individual rather than another is attacked. As in other diseases chiefly familial, cases occur sporadically, and no doubt some of the forms of persistent brawny œdema of the legs, beginning in childhood or early adult life, belong in this category.

Absence of all Local and General Causes of Œdema.—There are no evidences of thrombosis in the veins, or of lymphatic obstruction, nor are any of the constitutional causes of œdema present, and the patients are usually in good health.

The Local Condition.—The legs alone are involved. The œdema may appear shortly after birth or the onset may be delayed until puberty or even until adult life. Once established it is permanent. The extent is variable; it usually stops at the knees, and may only involve the ankles. In long-standing cases the swelling reaches the thighs, and the feet and ankles become œdematous, as shown in the accompanying figures (Plate XIX). The swelling is painless, increases in the standing posture, and naturally tends to become very hard and brawny. The veins are not enlarged, and there is no redness. By careful bandaging the swelling may be kept under control, and a patient may do hard work until an advanced age.

Acute Attacks.—In many cases, particularly noticed in the Hope-French series, there are remarkable attacks (usually following the onset of the œdema), possibly angioneurotic crises such as occur in the ordinary angioneurotic œdema. The following is a description of one of these attacks:

"It began on July 6, at 6 A.M., with a shivering fit which lasted until 8 A.M. She vomited, complained of headache, and had a pain along the outer aspect of the right thigh. At 9 A.M. her temperature was 101°. At 4 P.M. her temperature was 103.2° and her pulse rate 116 per minute. Her visceral systems all seemed natural. Her right foot was red and swollen. An irregular circle of redness, about nine inches wide in front and two inches wide behind, surrounded the right calf, and felt much hotter to the touch than did the surrounding skin. It did not project like erysipelas. The veins on the thigh and leg became unduly visible, but they were not prominent. A single lymphatic gland, not very big, could be palpated in the groin, and little pellet-like nodules could be felt in the skin around the reddened area. Next day, July 7, the temperature was 102° and the pulse rate 96 per minute. The redness of the right leg was more general, the foot more swollen, and a red patch was present over the patella. The patient was very sick, being unable to keep even water in her stomach. On July 8 the temperature was 98.4°; the swelling and redness were still present, but considerably diminished. On July 9 the leg and foot were still swollen and faintly red, but not painful. The red patch that had been on the calf was surrounded by minute raised spots, bright red in color, discrete, and rounded. On July 10 the leg began to ache during the afternoon; during the night it "burned," and on July 11 it was red and swollen, as at first. By July 16 the redness and pain had almost gone."

Diagnosis.—The diagnosis is never in doubt, once the family character is established, and the absence is determined of all the ordinary causes of œdema—cardiac, pulmonary, renal, leukæmic, or local in the pelvis, veins, or lymphatics. A point to which several observers have called

attention is the existence of other nervous troubles in members of the family, as epilepsy, insanity, or imbecility.

Treatment.—The acute attacks require opium for the pain, and locally, soothing lotions to the legs. It is doubtful if anything can control the tendency to the œdema. By far the most successful measure is persistent bandaging, which keeps the swelling in check. This was well illustrated by several members of the family described by Hope and French, who had in this way kept the swelling under control and lived for more than sixty years. Unless bandaging is done, the œdema gradually extends, and when it reaches the extent shown in the figures, it is impossible to do much for it.

CHAPTER XXIX.

DIFFUSE SCLERODERMA. ERYTHROMELALGIA.

By WILLIAM OSLER, M.D.

DIFFUSE SCLERODERMA.

Definition.—A nutritional disturbance of the skin, patchy or diffuse, leading to induration and atrophy. The pathology is unknown, but it is usually considered to be a trophoneurosis.

A local and diffuse form is recognized; the latter only is here described.

Incidence.—The disease is more common in the United States than the published reports indicate. From May, 1891, to May, 1905, I had under my care 18 cases, and I saw incidentally 2 others. To May, 1905 (a period of sixteen years), there had been 18 cases of scleroderma in the medical wards of the Johns Hopkins Hospital. The cases are more numerous in the general medical and the departments for diseases of the nervous system than in the dermatological clinics. Crocker states that of 10,000 cases of skin diseases in out-patient practice, there were only 8 cases of scleroderma: 2 diffuse and 6 circumscribed. It is more common in some countries than in others. It is stated to be rare in Germany. Lewin and Heller in 19,000 patients and 1800 skin cases saw only one instance of scleroderma. At the Vienna Dermatological Society in 1902, Neumann made the remarkable statement that scleroderma had only been known in that city for eighteen to twenty years, and that Hebra "had never seen a single case!" In Oppenheim's clinic, in Berlin, among 7000 cases of diseases of the nervous system there were 7 cases.

Etiology.—*Sex.*—Women are more frequently affected than men, 67 per cent. in the collected cases given in the monograph of Lewin and Heller (1895).

Age.—A majority of the cases are between the ages of twenty and forty years. A considerable number of cases occur in children, in whom the disease is more apt to be acute.

Heredity.—In a few cases, members of the same family have been attacked. A woman, aged twenty-eight years, had a brother and a mother who had had the disease, and Cassirer gives four or five cases from the literature in which relatives were affected.

Acute Infections.—These are believed to play the most important role in the etiology. Cases have followed influenza, acute otitis media, diphtheria, pneumonia, typhoid fever, erysipelas, scarlet fever, tonsillitis, tuberculosis, and syphilis. In several of my cases the disease was supposed to begin with rheumatism, but the joint troubles were really the initial symptoms. In one the severe arthritis antedated the scleroderma five or six years—the joints were swollen, hot, and red, and there were several attacks before the final one in the elbows and wrists, after which the scleroderma began.

The cases after the infections have often been more acute, and large areas of skin may be involved in a few days. In a few cases the disease has followed a septic puerperium.

Among favoring causes which have been mentioned are disturbances of menstruation, neuropathic disposition, protracted cold, emotional disturbances, trauma, psychical shock, migraine, alcoholism, etc. In looking over the histories of the eighteen cases in my series, it is not possible to say that there was any one etiological factor of special moment. That in two or three cases the symptoms followed an acute infection may have been quite accidental. In a majority of the cases the disease attacks healthy persons who had had only the ordinary wear and tear of life.

Pathology.—In only one case of the series, No. X (Julius Friedenwald's patient), did I have an opportunity of having a postmortem examination. Dr. Flexner made the autopsy, and the histology was very thoroughly studied under his direction by Dr. Bates Block. The following is a summary: There were no evident changes in the brain or spinal cord. The hypophysis was normal. The thyroid gland was healthy. The adrenals showed central cavities, due to hemorrhage, but no finer alterations. The arteries showed extensive arteriosclerosis (he was a man of forty), with marked thickening of the walls of the small vessels, and atheromatous changes and areas of calcification in the aorta and femorals. The peripheral nerves showed thickening of the connective-tissue sheaths, but no alteration in the fibers themselves. The skin presented the changes which have been so often described—sclerosis of the arteries, particularly of the smaller ones, which showed endarteritis and in places obliteration. There was an increase in the elastic fibers below the papillary layer, extending into the subcutaneous tissues. The connective tissue was present in coarse homogeneous bands, running parallel to the surface of the skin. This formed a hard, dense layer, measuring from 3 to 4 mm. in thickness. There was some hypertrophy of the smooth muscle fibers of the skin. There were no extensive changes in the muscles, but here and there were areas of fibrous invasion very different to the normal structure.

Practically these are the changes which have been described by all authors who have written on the subject, but we do not know how far they are primary, or whether they are secondary to undiscovered lesions in the nervous system. We have no clue as yet to the essential nature of the disease. The analogy of myxœdema, to which scleroderma is the cutaneous antithesis, suggests that it may be caused by some alteration in an internal secretion, or some disturbance of that nice balance between the various internal secretions of which we are just beginning to learn, and which seems to play such an important role in nutrition. The disturbances in pigmentation, as intense as any which we see, may depend in some adrenal inadequacy. The frequency with which the acute forms follow an infection is paralleled by the thyroid insufficiency and atrophy caused by myxœdema after a fever such as measles or scarlet fever. There are a few cases, as the one reported by Grünfeld, which suggest strongly thyroid disease, and in his case a cure followed the use of thyroidin, but it cannot be any simple inadequacy or more uniform results would follow this plan of treatment.

The view that scleroderma is due to a terminal endarteritis, which has been much advocated, has the anatomical basis of the widespread vascular changes which have been met with in every autopsy. Dinkler regards it

as an interstitial inflammation consecutive to the arterial disease. Lewin and Heller and many others regard the disease as an angiotrophic neurosis depending upon unknown changes in the trophic centre. These are the three important theories which have been advanced, each one of which only serves to throw into stronger relief our real ignorance of the true pathology of this remarkable disease.

Distribution.—The face and extremities are most frequently involved. Of the 420 cases collected by Lewin and Heller, the upper extremities were attacked in 287, the trunk in 203, the head in 193, and the lower extremities in 122. In only 3 cases in my series was the face not involved. A universal scleroderma is rare, occurring only in 16 per cent. of the cases.

Symptoms.—There are three modes of onset—the simple atrophic, the œdematous, and the erythematous. The *atrophic* is the most common. Case X of my series illustrates it very well, and gives a good picture of the course of the disease in a severe case. S. G., aged forty years (seen with Dr. Julius Friedenwald), a healthy man, of good habits, began to notice in October, 1897, that his hands were a little stiff. In January, 1898, some of the nails festered at their bases, and his hands would get red and blue. In November his legs felt stiff, and he went to Hot Springs, Va., for rheumatism. The feet became blue and swollen, so much so that he had to wear larger-sized shoes. He began to feel the cold very much. When I saw him in April, 1898, his face looked smooth, and the skin was everywhere firmer than normal. Both hands were congested, and felt firm and cold. There were scars at the roots of the nails and on the pads of several of the fingers. It was impossible to pick up the skin on the back of the hands. The feet were in the same state. The skin of the arms, legs, and trunk was not involved. He had lost thirty pounds in weight in six months. During the next four months the disease progressed rapidly, and by October 1 had involved the skin of the entire body. The movements of the limbs were much restricted, and, although looking natural, the skin was everywhere tense and firm. He had constant pains in the arms and legs; the nerves were not tender, nor were the joints swollen. The face was shrunken and mask-like, and he moved the lips with difficulty. The temperature was always about 101°, sometimes reaching to 103°. Through the winter he got progressively worse. The sclerosis of the skin of the trunk became extreme. He could move neither head nor limb, nor could arm or leg be flexed. He could scarcely open his mouth, and the face had become mummified. He wasted rapidly, and the whole body was as rigid and stiff as a statue. The back became bowed, so that the trunk could not be extended. He had recurring attacks of diarrhœa of great severity. During the last months this poor man presented an appalling picture—literally a breathing mummy. He retained his intelligence until near the end, which came March 14, 1899, less than two years from the onset of the disease. In two other cases which showed this atrophic type from the outset there was extreme pigmentation.

In only one case in my series was the onset with *œdema*, in the midst of which were depressed areas compared by Erasmus Wilson to the effect produced by pressing the finger into a bladder filled with lard. A girl, aged fourteen years, was seen with Dr. Pole November 11, 1900. In July she had had pains in the knees and ankles, and was in bed five weeks. In September she again had pains in the joints, and the legs became swollen, and Dr. Pole noticed the peculiar depressed spots. When I saw her the

legs to the knees looked swollen and œdematous; the joints were normal. On both there were remarkable depressed areas (shown in Plate XX, Fig. 1), as if the œdematous skin had pressed upon something. On the outer aspect of the left leg were four of these depressions, the larger one 6 cm. in length. These areas had a slight purplish discoloration. The skin in the intervals between them was raised and of white color. To the touch, the skin was everywhere smooth and hard, that in the depressed areas impossible to pick up, and a firm ridge could be felt at the margins. The swollen skin between the patches was not so hard, but was infiltrated, although it did not pit. Both the mother and patient stated that the trouble began as raised red areas, corresponding to those now depressed, and at a subsequent visit I saw three of these spots—one 1.5 cm. in diameter, the others 2.5, raised, erythematous, and tender. In this case the skin of both legs was swollen and looked œdematous, although it did not pit at any point. Once formed, the depressed areas gradually extended, and although there was a very definite ridge, there was never any redness. Several of the patches coalesced, and large areas of the skin became sclerotic and of a light brown color.

The *erythematous onset* is of two types: in one, a diffuse erythema and swelling occurs in the face or in parts of the trunk; in the other, the picture is that of the vasomotor disturbances of the hands and feet, like Raynaud's disease.

In Case XV the erythema and swelling were more marked than in any one of the series. S. J., aged forty-seven years, a healthy man of good habits, was seen December 29, 1900, with Dr. Urban Smith. The trouble began three years before, with swelling of the face and of the left wrist and arm, and these parts would be at times so red that he had to remain at home. The hands became painful, and within the last year the skin of the chest has become red and swollen. When seen the face was smooth, without wrinkles, and the skin everywhere parchment-like. The entire neck was hidebound. Over the front of the chest the skin was reddened, a little darker than normal, and swollen. Toward both axillæ there was a distinct line of demarcation. In the upper part of the axillæ, and extending over the scapular regions, there were the same erythema and swelling. The hands were sclerotic and stiff. The anterior surface of both forearms was swollen and red. I followed this case for more than two years. The general sclerosis became more marked, and the hidebound condition was universal. The hands and feet became purple. I never saw more persistent or deeper cyanosis; it took more than thirty seconds to obliterate the anæmia of a finger mark. Toward the end he had remarkable attacks of tachycardia. He died five years from the onset of the disease.

In several cases the onset was with symptoms suggestive of Raynaud's disease, so much so that in Cases XI, XVI, and XVII the diagnosis of this affection was made. In Case XVI, a woman, aged thirty-two years, the hands and fingers became swollen and red. "At times they were more blue than red, and again they would be perfectly white and cold. Usually all the fingers would be affected, but the middle right finger was the most frequently involved. The change in color to white, blue, and red occurred within a few hours. These attacks came on irregularly, at intervals of about a month." Could anything be more typical of the onset of Raynaud's disease? This patient had a most severe attack, with widespread involvement

PLATE XX

FIG. 1



Scleroderma with Œdema, showing depressions.

FIG. 2



Scleroderma with Local Panatrophy of the Left Arm.

of the skin and the most extensive pigmentation, and death followed three and one-half years from the onset. In Case XVII, also a most severe, diffuse form, "he first noticed that the fingers and hands would become purple or almost blue; then at times they would be swollen and white. They were much worse in cold weather." In Case XI, a woman, aged twenty-eight years, the disease began with local asphyxia of the fingers and toes. As it was winter, she thought at first they were frostbitten. The pads of the fingers split open and were very sore, and the feet became so swollen and tender that she could not walk. In the summer she was better; then as the cold weather came on the hands and feet would ache, and, as she expressed it, she was "half crazy with the pain," and at times the fingers and toes got so black that gangrene was feared. I saw her four years after the onset of these symptoms, and she then had well-marked features of scleroderma. The movements of the face were restricted, the nasolabial folds were obliterated, and the nose had become sharper. The skin, which could not be picked up, was hard and parchment-like. The hands and feet had a natural color, but they looked large and flabby. The middle finger of the right hand was cyanosed. The movements of the fingers were stiff, and she could not pick up small articles easily. The hands felt cold, and the skin was everywhere firm. The pads of the fingers were puckered and scarred. I saw this patient at intervals for nearly three years, and she had a very thorough treatment with thyroid extract, with decided benefit. For a time the face was worse, but the skin became softer and the hands were less stiff.

Several writers have called attention to the onset with arthritis, and in my series there were three cases in which this was a special feature. Thus, in Case XVII, following a severe attack of influenza in March, 1898, the joints began to be painful and stiff, and by June nearly every joint in the body felt sore, although there was neither swelling nor redness. In another case severe attacks of arthritis occurred at intervals for three or four years before the skin was affected.

In many cases the earliest stage is an œdema, with slight efflorescence, a firm, solid infiltration which does not pit. The appearance is not unlike the erythema of leprosy, and I saw a case at the dermatological section of the British Medical Association, in which a number of distinguished specialists were in doubt which of these two conditions was present. It may be diffuse, or in small patches, and in Case XIII of my series there were raised spots not unlike erythema nodosum. It may last for weeks or months. Then the skin begins to get hard and tense, the stage of induration, and the color changes to a dead white, or it has the tint of old marble or of parchment. The consistence changes, and it feels firm like a bit of frozen skin, and it may be impossible to pick up a fold. This is a very characteristic test, as everywhere, even in the fingers, the normal skin can be picked up in folds. In some cases there is not a bit of skin that can be pinched between the finger and thumb. The folds are obliterated, the wrinkles disappear, and the face has a mask-like aspect—Gorgonized. The face grows smaller, the lips thin, the nose pointed and narrow, the cheeks smooth, the ears shrunken, the eyes expressionless, and the diagnosis may be made at a glance. The hands look smooth, the fingers are semiflexed, the terminal joints may be shrunken and involved in a sclerodactylism of the most advanced type. The hands are converted into rigid, immobile organs. In severe cases the unfortunate victim is as though he

had been put in the fabled shirt of Nessus, which had gradually contracted upon him. The back is rigid, the neck is fixed, and he may resemble a frozen corpse or a mummy, without the power of motion, save in eyes and tongue, which alone gives witness to remaining life.

As the disease progresses three changes occur: (1) Atrophy follows the induration and the skin becomes thinner, although not softer. At the lines of extension this gives a ridge in which three zones may sometimes be seen: an inner, yellowish brown, corresponding to the atrophic portion; a white, indurated portion; and beyond it a narrow zone of erythema. In the gradual extension, weeks or months may elapse before a distance of an inch is covered. In other cases, by the coalescence of contiguous areas, large portions of the skin may be involved. The atrophied skin may gradually grow more natural looking and softer. (2) The second change is in the involvement of the subcutaneous tissues, which become sclerotic and bind the skin tightly to the subjacent parts. The mobility of the skin is in this way lost, and it can no longer be moved freely upon the muscles or bones. When atrophic and smooth the skin may fit on the bones of the hand like a glove. (3) And the third change is in the color, most frequently an increase in the pigmentation, giving to the skin a parchment-brown appearance. My series afforded most interesting studies in this change, which I have dwelt upon fully in my paper.[1] There may be the muddy brown discoloration which is common in the atrophic areas, or there may be a curious mottled or freckled appearance, such as we see so often in the arsenical pigmentation about the abdomen. But the most remarkable instances are those in which the entire skin becomes of a deep brownish black, like the most extreme form of Addison's disease. In Cases VIII and XVI the diagnosis of suprarenal disease was suggested, and I do not know that there is any other condition in which we meet with a more intense melanoderma.

Atrophy of the pigment causing areas of leukoderma almost always accompany the pigmentation. They are well shown in the colored plate illustrating my paper. In the midst of almost black areas there may be scattered patches of normal looking or dead white skin. On the abdomen the alternation of lines with hypertrophy and atrophy of the pigment may present a very curious appearance. In Case IX the inner aspects of the thighs and the popliteal spaces were very dark—in fact, as black as the skin of a negro. This had come on gradually, as the disease had extended. In the atrophic areas the pigmentation became very intense, but within two years it had changed to a light brown, and here and there were a few spots of leukoderma. In none of my cases was there pigmentation of the mucous membranes.

An interesting change in the sclerotic skin is the development of telangiectasis. The following is the note on a case, No. II, a very chronic one, in which they did not occur until the fifth or sixth year. They gave a most unusual appearance to his face. "Everywhere on the skin of the face are spider angiomas of a bright red color, varying in size from 3 to 5 mm. On the forehead, nose, and cheeks they are very thickly set; on the bridge of the nose are several very large ones. There are none on the mucous membranes of the mouth or nose. Each one has a central vein, with three to five branches and a deep red capillary zone. On the extensor surface of the left wrist

[1] *Journal of Genito-urinary and Skin Diseases*, New York, 1898.

is a large 'mat-nævus,' 4 x 5 cm. in diameter, of a deep rose color, which disappears entirely on pressure, and the backs of both hands are covered with the smaller variety." These have all appeared within the past two years. It is interesting to note the similarity in appearance of these telangiectases to those in the sclerotic tissue of the *x*-ray burns.

The secretory functions of the skin may be undisturbed. In several of my patients there was hyperidrosis, and the skin of the hands and feet was always moist. When touched, the hard, cold, clammy sensation of the sclerodermatous hand feels like that of a corpse. There is no special change in the secretion of the sebaceous glands. The skin is not often dry and scaly.

Trophic changes other than the scleroderma itself are not uncommon. Several of my patients had local suppuration about the nails, and in Lewin and Heller's collection there were forty-eight with *ulcers* about the fingers or knuckles. They have occurred in my series either in the early stages in connection with the vasomotor changes, or late when the knuckles and finger-joints were hidebound. Sclerodactylism is a not uncommon event, occurring in three of my eighteen cases. It comes on gradually with or without previous local asphyxia and trophic changes in the pads of the fingers. In Case II, at the end of the fifth year both hands presented a typical condition of sclerodactylism; he could not make a fist, the motion at the metacarpophalangeal joints was very slight, and there was complete immobility of the first and second joints of the fingers; the thumbs could be opposed to the first and second fingers, so that he could still use his hands to dress and undress himself. The fingers were bent and the terminal phalanges at right angles to the others. There was a gradual wasting of the end-joints, which were thin, pointed, and about half the length of an ordinary phalanx. The nails were curved, ribbed, and shortened. There were scars over all the finger-joints, and on the knuckles there had been troublesome open sores.

The hair may fall out from the sclerotic skin or get very thin, and this seems the usual course; in a few cases with the pigmentation there is an increase in the growth of the hair, as is very well shown in the colored plate illustrating my paper. Loss of the pigment of the hair has been observed.

Trophic changes may occur in the deeper parts. The *bones* may be affected, and, as in Case XIV of my series, all those of the left upper extremity, including the scapula, were atrophic. More often the change is confined to the fingers. In a few cases local hypertrophy of bone has been observed, thickening of the tibiæ or of the malar bones. The *muscles* beneath the sclerosed skin may be involved. The deltoid and anterior group of muscles of the forearm were hard and fibroid in Case XIV. Muscle atrophy has been described in connection with sclerotic changes in the skin covering it; in other instances the muscle has been sclerotic beneath a normal skin. A widespread myositis has been met with in connection with scleroderma of the thorax and nates (Kaposi).

How far the *joint troubles* of the disease represent an arthropathy is a question. They are common, particularly in the early stage. There may be pains alone, and disability from this cause. In one of my cases there was inflammation of the right ankle for weeks before the onset of the scleroderma in the hands. Deformity and osteophytes have been met with,

but, as a rule, it is a painful arthritis of onset. Subsequently the joints become fixed by the sclerotic skin, and toward the close not a single joint of the body is mobile. In the postmortem in Case X no changes were found in the joints.

Changes in sensation are not common; numbness and tingling may be present, but there is not often pain, except when the disease begins with the features of Raynaud's disease. Case XVI had severe pains in the hands and feet. As a rule, scleroderma is a painless affection and sensation is well preserved, even in the atrophic skin. In the early stages, as was well marked in Case XIII, the acuteness of the sensation was duller in the affected areas. There may be great sensitiveness to cold, and, as a rule, the patients are more comfortable in summer.

The general health may remain very good. Case II, Levi B., came back year after year to the clinic, and although his face, hands, and legs were affected, he was very comfortable, and could even dress himself. The erosions over the knuckles gave him the most trouble. In the severe cases a cachexia comes on, the patient gets thin, there is fever, diarrhœa, and death follows from exhaustion. One of my patients died suddenly, another from pneumonia. Fever is not a constant feature; as the sclerosis progresses actively there may be a degree or more, but, as a rule, the course is afebrile. The pulse is usually unaffected. In two of my cases there were attacks of tachycardia. Arteriosclerosis may be present, but there may be extreme scleroderma without much, if any, change in the arteries. No special changes have been met with in the heart.

Blood examinations were made in eight or ten of my cases. There were no special alterations. In Case XVI the leukocytes were 10,500 per cmm., the eosinophiles 3.3 per cent., and the small mononuclears 19 per cent. In Case XVII the eosinophiles were 2.4 per cent.

The urine is, as a rule, normal. Albuminuria is present in a few cases; sugar has been detected.

Association with Other Diseases.—A number of cases have been reported of scleroderma in Graves' disease. One patient in my series presented a typical instance of this combination. It is usually of the legs, and not often generalized. Thyroid enlargement has been present in a few cases, and the association with atrophy has been noted.

One of the greatest difficulties is in the association with Raynaud's disease—whether the scleroderma begins as a complication of this affection or whether the local asphyxia and trophic changes may be regarded as part of the scleroderma. In five of my cases the vasomotor changes were most marked; in two the symptoms of onset were those of Raynaud's disease. The case reported under modes of onset is most typical, and Case VI presented very similar symptoms. In none of the cases did the asphyxia pass on to severe gangrene, although there were superficial losses of substance. The vasomotor changes in the disease are extraordinary. In Case VII there was the most remarkable vasomotor ataxia I have ever seen—the cyanosis of the legs when he stood up was most extreme—they became plum-colored in half a minute; when on his back and the legs held up the skin at once became anæmic. One could literally see the blood fall into the legs when he stood up. The same extreme cyanosis was present also in another case.

Cassirer makes a good division of the cases with these marked vasomotor

phenomena: First, instances of Raynaud's disease, in which in the late stages, besides the gangrene, there are trophic changes in the skin of the fingers and hands, which become smooth, glossy, and hard; the fingers may be immobile, and a well-marked state of sclerodactylism is produced. The process is limited to those parts which have been frequently the subject of attacks, and there is no extension to the arms or legs or trunk. Secondly, cases in which the scene opens with marked vasomotor changes—local syncope and asphyxia, and acroparæsthesia. Gradually, without progressing to local gangrene, these symptoms are succeeded by a typical scleroderma, which is not limited to the parts which have been affected with these vasomotor changes, but extends widely. Thirdly, there are the rare cases in which in a typical sclerodermic case Raynaud's symptoms supervene with gangrene.

Local Panatrophy in Scleroderma.—In Case XIV the entire left arm was atrophic and the skin sclerosed; some of the muscles were firm and hard. Plate XX, Fig. 2, shows the condition very well. The patient was aged fifteen years, a strong healthy boy. When seven years old the mother noticed that the left wrist was a little stiff, and from that time he has had constant trouble with the arm, in which there has been a progressive disability without pain. The whole extremity was involved, the left shoulder blade being smaller than the right. There was a difference of an inch in the length of the limbs; the left was atrophic, and the hand smaller; as shown by the radiographs the bones were much smaller. The skin of the forearm was hidebound, in places pigmented; that of the arm was thin and wasted. The muscles of the forearm were hard and firm, very different in consistence to those of the other side. The biceps was hard and fibrous, while the triceps was soft. There was a definite line of demarcation between the normal and diseased skin extending over the pectoral fold in front, the clavicle, and obliquely down the back to the posterior axillary fold. There was an isolated patch at the root of the neck on the left side, 6 x 5 cm. in extent, sharply defined, and the skin was pigmented and thin. The movements could all be made, but the flexion and extension of the wrist were restricted. The fingers were not sclerotic, but the skin was in some places thin and glossy, in others pigmented. The condition was very like the local panatrophy described by Gowers and by Harry Campbell. In Gowers' case, a woman, aged thirty-three years, "presented in certain areas of the trunk, limbs, and face areas of wasting of all the subcutaneous tissues down to the bone with thinning and discoloration of the skin. They were irregularly distributed without apparent relation to muscles or to nerve distribution." One patient, aged thirty-two years, had atrophy about the shoulder, with wasting of the skin and involvement of the subcutaneous tissues and muscles, and in one place the bone also was atrophied.

Course and Prognosis.—There are acute and chronic forms. The acute cases are usually in children, and have followed an infection. In the *Archiv f. Dermatologie*, 1900, Band li, Müller reports a case in a girl, aged sixteen years, coming on six weeks after otitis media. In three days the arms, cheek, back, and neck were as hard as wood, and the head was immobile. The skin could not be pinched up. The face was only slightly involved. There was no disturbance of sensation. The affected regions were tender to the touch. In Marsh's case, a two-year-old child, the acute onset followed diphtheria, and within two weeks the hands and face and trunk were involved. Some of these cases have subsequently had a chronic

course. In the most rapid case in my series, No. X, death occurred within two years. As a rule, the course is very chronic. Lewin and Heller found ten cases in which the disease had lasted more than fifteen years; one of these had a duration of forty-eight years, another of thirty. The longest case in my series, Levi Bear, well known to so many of the graduates of the Johns Hopkins Medical School, has had the trouble for more than fifteen years. The disease became stationary after about five years' duration.

The arrest may leave the victims in the stage when they are fairly comfortable, or there may be great disability. In Case XII, a woman, aged forty-six years, the scleroderma began in 1898, and when I saw her in 1900 there were extensive areas of pigmented and atrophic skin in the abdomen and thorax. In the lateral regions of the chest there were areas of erythema, with slight swelling, and there were efflorescences at both elbows and on the anterior surface of the arms. In places the skin was very hard and impossible to pick up. The hands, feet, and face were not affected. Four years later the disease had made no further progress, but the patches of erythema had disappeared. The skin of the affected parts was thin, pigmented, and closely adherent to the adjacent tissues. In two other cases the disease seems to have been arrested. In no instance in the series did complete cure take place—an experience which does not bear out the hopeful view of some dermatologists, Crocker, for example, who says, "The disease, as a rule, tends to get well spontaneously." Lewin and Heller give 16 per cent. of recoveries. The outlook in children is better even in the acute cases; the percentage here in the statistics of these authors is 31. Recovery has followed in a month or six weeks. The cachexia carries off a majority of the patients; others died of bronchial, renal, or pulmonary complications. Death may occur suddenly.

Diagnosis.—Dermatologists recognize two forms of the disease—a local, often called morphœa, and the general or diffuse. Hutchinson makes an interesting classification of the cases—an herpetiform, which, like herpes zoster, is distributed in bands and streaks, and may be bilateral; an acroteric, beginning in the extremities with symptoms like Raynaud's disease, and leading to acroscleroderma; and lastly, a generalized scleroderma, a hidebound condition of the skin. The local disease presents identical anatomical characters, but there are certain differences—it often follows nerves, distributed accurately in their course. Lewin and Heller have collected many cases illustrating this. In a patient of Brissaud's the sclerotic bands corresponded accurately to the seventh and eighth cervical segments, the first and second dorsal, the fifth lumbar, and the first sacral segments. There is a much greater tendency to complete recovery; pigmentary anomalies are not so common; and sclerodactylism does not occur. The local form may occur on arm, leg, or trunk, less often in the face. It begins in the manner already described, and only the limitation in area separates it from the more severe form. A case may start in one or two spots, and gradually spread and become diffuse.

The diagnosis is rarely in doubt. In not one of the cases in my series was there any difficulty in recognizing the existence of scleroderma, but in two the question arose of the co-existence of Raynaud's disease, a point which has been discussed sufficiently under the symptoms. The sclerodactylism may suggest syringomyelia, but the absence of sensory and other changes is sufficient to differentiate the two conditions.

The local panatrophy of Gowers resembles scleroderma, and some of the cases, as I have mentioned, may be this disease. Only in the early stages do the cases offer any difficulty. The preliminary erythema and infiltration may strongly suggest leprosy, and I mentioned a case shown at the British Medical Association in which different opinions were expressed. A point of moment is that the sclerodermatous erythema is never extensive for a long period without the other changes; the hard œdema begins to disappear in places and the skin atrophies and changes in color. On the whole, generalized scleroderma is a disease easy of recognition. A glance at the face or the hands may suffice; difficulties only rise in a few rare instances when the vasomotor disturbances are extreme and when the local asphyxia leads to changes suggestive of Raynaud's disease.

Treatment.—I doubt if any remedy has an influence on the course of the disease, unless it be the *x*-rays, which, with the new and more accurate methods of application, should be given a thorough trial. In the acute cases hot baths and massage should be tried, and in all forms systematic hydrotherapy should be used. Massage is helpful, and in any case keeps the skin softer and promotes nutrition. These measures with electrical treatment should be carried out thoroughly as early in the course as possible. A stay at one of the baths, Hot Springs, Va., or Mt. Clemens, or one of the alkaline and sulphur baths in Europe, should be advised. Of remedies, I have given a very thorough trial to nearly all on the list, the iodides, salol, and the salicylate preparations, and the various thyroid preparations. In my paper describing the first eight cases of my series I give the details of six cases treated with thyroid extract. Of the remaining ten cases, nearly all received a full trial of this remedy. Possibly to it the arrest in three or four of the cases may be attributed, but in Case X the disease made rapid progress under its use; and the best that can be said is that in some cases it appears to retard the progress. The remedy is well borne for years in doses of grs. v of the extract three times a day. I saw no ill result. In neither of the cases in which tachycardia occurred was this due to the extract. It is well to omit the use for a week or ten days at the end of each period of six or eight weeks. Various other thyroid preparations were tried without any special effects. Thymus extract, adrenalin, and suprarenal extract were also used. I have seen no report of the use of fibrolysin —but scleroderma would be an ideal disease in which to test its claims.

ERYTHROMELALGIA (WEIR MITCHELL'S DISEASE).

Definition.—"A chronic disease in which a part or parts of the body, usually one or more of the extremities, suffer with pain, flushing, and local fever, made far worse if the parts hang down" (Weir Mitchell).

Introduction.—In 1872 Weir Mitchell described in the *Philadelphia Medical Times*, under the title "On a Rare Vasomotor Neurosis of the Extremities," a peculiar red neuralgia. In 1878, in the *American Journal of the Medical Sciences*, he still further elaborated his views on the subject. Other papers by him are to be found in the *Medical News*, 1893, and the *American Journal of the Medical Sciences*, 1899 (with Spiller). He gave to the condition the name erythromelalgia, signifying a painful red state of a limb.

Cases had previously been described by Graves, Paget, and others. The literature is very fully given in Cassirer's monograph (*Die Vasomotorisch-Trophischen Neurosen*, Berlin, 1901) and in the *Index Catalogue*, Series II. Much discussion has taken place as to the existence of erythromelalgia as a separate disease, apart from Raynaud's disease, affections of the spinal cord, obliterative endarteritis, and the various forms of peripheral neuritis, in all of which pain and redness of the extremities may occur. These conditions should, I believe, be excluded, and the name limited to a vasomotor neurosis with the features above given, a small but perfectly definite group of cases.

Etiology.—The disease is rare. I have seen only one case in private practice in which the diagnosis seemed clear. At the Johns Hopkins Hospital in twenty years (to 1909) there were three cases.

Cassirer has collected 90 observations which have been reported as erythromelalgia, but a great majority of these belong to other conditions.

Age and Sex.—Men are more subject to the disease than women—46 to 32 in Cassirer's figures. His age table is: from one to ten, 2 cases; eleven to twenty, 2; twenty-one to thirty, 21; thirty-one to forty, 13; forty-one to fifty, 11; fifty to sixty, 12; sixty to seventy, 2; above seventy, 2. Graves' case was in a woman aged eighty-two years; Henoch's in a teething child.

Among *predisposing causes*, puberty, menstrual disturbance, and the climacteric are mentioned. In a few cases the disease has followed an infection—rheumatic fever, gonorrhœa, syphilis. Cold and damp are important *exciting causes*. Weir Mitchell's first case was a sailor who had been much exposed; Elsner's patient had had to do a great deal of washing; Paget's patient was much given to cold douches and hydrotherapy, standing with the feet in cold water. In several cases the disease has come on after exposure. In my case the girl got her feet wet and had to sit for some hours without changing. Overexertion or a sudden strain has been an important factor—overuse of a hammer, prolonged use of the legs in working a sewing machine, or a protracted march. In a few cases a blow or an injury to the limb has preceded the onset of the symptoms. Several cases have been in highly strung neuropathic individuals.

Pathology.—Cassirer, whose study of the condition is very thorough, recognizes two groups of cases of erythromelalgia—one in which the symptoms are localized in a definite nerve territory, the other in which they are distributed over the distal portion of a limb. The first group has many points of resemblance to neuritis, but may exist without the positive signs of neuritis, anæsthesia or other disturbance of sensation, disturbance of motion, or painful points along the course of the nerve. In the second group no basis exists for the diagnosis of any special lesion, arterial, neuritic, spinal, or cerebral; although from the distribution and general features we may suppose that in the one the trouble is peripheral, in the other central. This is about as far as our knowledge goes of the pathology of erythromelalgia, and it is not very far! The postmortem reports are not in accord: "Once changes were found in the peripheral nerves (Weir Mitchell and Spiller); once changes in the posterior roots (Auerbach); in three cases the peripheral nerves were intact (Weir Mitchell, Dehio); the arteries were found diseased in three cases (Sachs and Wiener, Dehio, Weir Mitchell, and Spiller)." Cassirer thus summarized the results. It is very probable that the cases with local distribution are due to changes in the peripheral

nerves; the symptoms resemble closely those caused by certain forms of peripheral neuritis. When the whole limb is involved the vasomotor centres are probably at fault, but what the nature of the change and where, we have at present no clue. The pathology will be found to be much the same as that of Raynaud's disease, with which erythromelalgia has very close affinities.

A more careful study of the nerve centres in cases of spinal cord and cerebral lesions associated with a congested and painful state of one or more extremities may throw some light on this dark chapter in neurology. The arterial cases should be cut out of the category altogether, as forming a separate and remarkable malady (with which we may well honor the memory of a good pathologist by associating the name of Friedländer) worthy of the most careful study. The researches of Erb and others have shown how common are these cases of endarteritis of the vessels of the extremities, and how diversified are the symptoms; one group has a striking similarity to the condition under consideration.

Symptoms.—Redness, pain, and swelling are the cardinal features of the disease. A very bright, healthy-looking girl, aged about twenty years, walked into my consulting room on crutches. When she removed the felt shoe and stocking from the left leg it was seen to be swollen and red, as high as the middle of the tibia. The toes were a little blue, but in a few minutes, as she rested on the sofa, they, too, had the vivid pink appearance of the foot and leg. The swelling was moderate and most evident about the ankle and tarsus. When she sat up and hung the foot down the redness became more marked, and the toes again became livid. If she attempted to put the foot to the ground she winced, and said it hurt very much, but on insisting she stood alone on the foot, but the pain increased and was chiefly in the sole and in the toes. In the recumbent posture the color was less intense and the pain ceased. When the foot was elevated the redness almost disappeared, but not entirely from the toes. To the touch the leg and foot were hot, and the temperature was 6° higher than on the corresponding parts of the other leg, much less than the hand suggested. It was nowhere painful on pressure, except at one or two spots in the sole, the worst near the heel and at the ball of the big toe. There was no pitting. The pulsation in the arteries was much fuller and more evident than in the sound leg. There was no tenderness along the course of the nerves. The veins were not visible except on the dorsum of the foot. In every other respect the girl was healthy. About three months previous she had got her feet wet, and had to sit for several hours without changing. In a few days she began to feel pain in the sole and toes of the left foot, but only when walking. Then she noticed the toes were of a bright red color. The condition has gradually grown worse, and extended first to the whole foot and now half way up the leg. She has very little pain except when she puts the foot to the ground, or if it has hung down for a long time. She is not disturbed at night, and her general health is excellent. Careful bandaging, rest, massage, and hydrotherapy were advised, but months passed without much change; then for no very obvious reason the condition began to improve, and about a year after I saw her she wrote that she was practically well.

Among the score or more of cases of painful red extremities that I have seen due to various causes—organic lesions of the spinal cord, endarteritis,

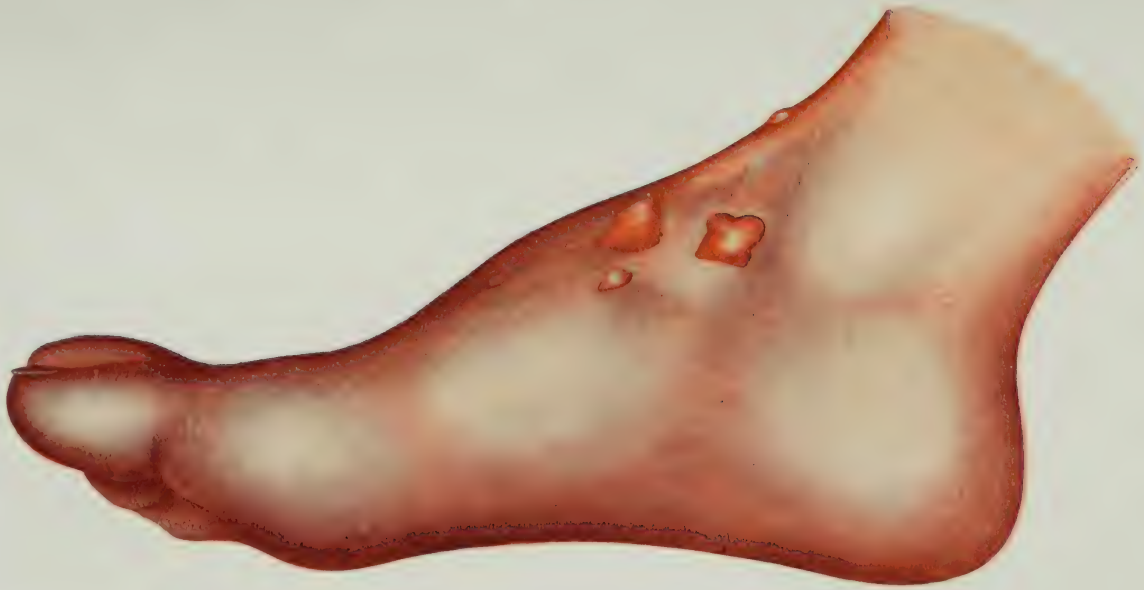
neuritis, and Raynaud's disease—this case stands out as the only one in which the diagnosis of erythromelalgia seemed justified.

Parts Affected.—The feet are most often involved. In Cassirer's analysis the involvement was: both feet, 20 cases; one foot, 7; both hands, 10; one hand, 3; all four extremities, 13; and hand and foot of the same side, 2. In 12 cases the pain and redness were limited to the distribution of a single nerve. The fingers and toes are usually involved first, and the trouble spreads upward, and may cause swelling of the lower leg or of the forearm. It rarely reaches above the elbow or knee, but the pain may extend to the hip or the shoulder. One or two toes may be affected for weeks or months before the disease extends, or the trouble may begin in the sole of the foot or the palm of the hand. After persisting for months or for a year or more in one foot it may extend to the other. In marked contrast to Raynaud's disease, the ears and nose are not affected. In a few cases painful red spots have appeared in other parts of the body, and Mitchell remarks that he has seen this distribution and suggests, indeed, that similar vasomotor disturbances may occur in the muscles and bowels. I have seen no case reported with abdominal colic, such as is so common in angioneurotic œdema, and occasionally in Raynaud's disease.

The most striking objective feature of a case is the *redness,* which in typical instances is the color due to an active hyperæmia—a deep pink or violet-red, diffuse, not mottled, and sometimes sharply limited above. The veins may be swollen, but the general appearance is that of an inflammatory congestion, not of a venous stasis. One of the most remarkable features upon which Weir Mitchell lays great stress is the influence of change of posture; when the foot hangs down the congestion increases at once; when placed above the level of the patient's body, as he is recumbent, it grows pale, and the congestion may almost completely disappear. Not that this is peculiar in any way to erythromelalgia, but one does not often see it in the acute hyperæmia. In the cold and in long-standing cases there may be blueness or asphyxia, but this is rare. The temperature is always higher, 4° to 6° or more, less than the hand suggests, as the affected part feels hot and the arteries of the foot may be felt to throb. *Pain* is almost always present, either an intense burning sensation or a sharp, stabbing sensation of a less continuous character. When at rest there may be nothing more than an unpleasant hot feeling, but on movement, as in attempting to put the foot to the ground, the pain may be severe. The slightest pressure with the finger may cause pain. Very rarely is the pain of the maximum intensity seen in Raynaud's disease. *Sweating* is a common feature, and it may be hyperidrosis. Thickening of the skin, pigmentation, and changes in the nails may occur. More or less swelling is almost always present, but there is no pitting on pressure. Disturbances of sensation are not common, but there may be hyperæsthesia or pain along the course of the nerves. *Atrophy* of the muscles of the affected part may occur, as in the small muscles of the hand or foot; occasionally, as in one of Mitchell's cases, the muscles of the affected leg may waste. In the protracted cases there is always some wasting from disease. Serious trophic changes leading to gangrene do not occur. The cases that have been described belong to the category of Raynaud's disease, or are due to obliterative endarteritis, and it may be very difficult to say in a given case which condition is actually present.

Diagnosis.—There are four chief conditions in which "pain, flushing, and local fever," to use Weir Mitchell's words, occur, and which may be confounded with erythromelalgia, or which may simulate it so closely that it

PLATE XXI



Erythromelalgia. Foot after hanging down for twenty minutes.

(Case of Dr. J. M. Taylor.)

PLATE XXII



Erythromelalgia. Foot after hanging down for thirty minutes.

(Case of Dr. J. M. Taylor.)

will depend altogether on the conception one has of the disease where an individual case is placed. I would limit the term to a small but well-defined group conforming clinically to Weir Mitchell's original description, and of which at present we do not know the anatomical basis. A "red, painful neuralgia" of an extremity may be associated with Raynaud's disease, with certain affections of the spinal cord, with endarteritis obliterans (Friedländer's disease), and with peripheral neuritis.

Raynaud's Disease.—Many cases simulate closely erythromelalgia, in others the two conditions appear to have been associated, or the one may pass into the other. Objectively, every case of Raynaud's disease becomes one of erythromelalgia in the stage of active hyperæmia, when the part is red and hot and painful, and yet typical cases have features which suffice to separate the two diseases, although it must be confessed by a very thin partition. Weir Mitchell's differential table may be given here:

Raynaud's Disease.	*Erythromelalgia.*
1. Sex—four-fifths females.	1. In 22 cases 2 were women.
2. Begins with ischæmia.	2. Little or no difference in color is seen until the foot hangs down in upright position, when it becomes rose-red.
3. Affected part becomes bloodless and white. In certain cases there is a deep, dusky congestion of a cyanosed part with or without gangrene.	3. The arteries throb and the color becomes dusky red or violaceous in tint.
4. Pain may be absent or acute, and comes and goes; has no relation to posture; may precede local asphyxia.	4. Pain usually present; worse when the part hangs down or is pressed upon. In bad cases more or less at all times.
5. Unaffected by seasons. In many cases all the symptoms are brought on by cold.	5. Worse in summer, and made worse by heat; eased by cold.
6. Anæsthesia to touch.	6. Sensations of all kinds preserved
7. Analgesia.	7. Hyperalgesia.
8. Temperature much lowered and unaltered by position.	8. Temperature above normal. Dependency causes in some instances an increase, in others, a lowering of the temperature.
9. Gangrene local and limited, and likely to be symmetrical.	9. No gangrene; lesion asymmetrical.

Some of the cases are very difficult to classify. Rolleston reports one in a man, aged twenty-nine years, who for a year had weakness in the hands and feet and for six months pain, and a great sensitiveness to cold, so much so that they would become swollen and red. If the parts hung down they throbbed, swelled, and "went dead." Even in summer the hands were swollen, red, and hot, and very sensitive to all sorts of impressions. At times they were very painful, and pains passed up the arms to the shoulders. The feet, too, were red and hot, and thick, and very sensitive. Both hands and feet were thickened and acromegalic in shape. What was this? Rolleston reports it correctly under the title "A Case Showing Some of the Features of Erythromelalgia and of Raynaud's Disease."

Elsner reports a still more remarkable instance in which the features of the two diseases were combined. A woman, aged thirty-eight years, had in the winter of 1893 numb feelings in the hands and headache. In the following winter there was burning in the palms and backs of both hands, and attacks of pain associated with an erythema of the hands and arms. In 1896 there was an increase in the pains in the hands to an intolerable degree,

with great sensitiveness of the parts, and copious sweating. In September, 1896, the redness disappeared suddenly from the thumbs. A red spot appeared in the right tragus, which passed on to asphyxia and gangrene. A second gangrenous spot appeared over the middle of the left sternocleidomastoid muscle. On the 16th of September cyanosis and gangrene of the top of the thumb occurred, with gradual separation of the phalanx; there was gradual recovery. Certainly, at first this would have been regarded as a typical instance of Weir Mitchell's disease, but three years later the severe trophic changes put it into the category of Raynaud's disease. The affections are closely allied, and it is not surprising that they should be associated or that the one should follow the other.

Affections of the Brain and Spinal Cord.—I have already spoken of the vasomotor and trophic changes simulating Raynaud's disease, which are met with in organic diseases of the spinal cord. A condition of painful erythema, with swelling, may occur, and many cases have been described as erythromelalgia. In hemiplegia the forearm and hand may become red, painful, and swollen, a vasomotor change very like Weir Mitchell's disease, and the condition may persist for months. I saw a hemiplegic whose hand and arm had been painful and the hand red and œdematous for more than six months; and at the Infirmary for Nervous Diseases, Philadelphia, I had a patient whose sufferings from this cause were atrocious. A number of cases have been reported in locomotor ataxia, and Collier has recorded five instances in multiple sclerosis. Altogether, Cassirer has collected 22 cases in this group. The clinical picture is often a vasomotor paresis, as in the hemiplegic arm, but it may resemble Weir Mitchell's disease very closely. One of Collier's patients was a woman, aged twenty-nine years, who had had multiple sclerosis for nine years, spastic paraplegia, etc. Two years after onset she had attacks of burning pain in both feet, with redness and heat, lasting three hours. A year later the feet were permanently red, and when the legs hung down they became red to the knees. Later, when she stood, the legs became purple and hot, the skin swollen, the veins distended, and the arteries throbbed and the legs and feet were painful. It is very difficult to say just where these cases should be placed. Some of them simulate erythromelalgia closely, others are more like Raynaud's disease, and others again have a dull, dusky congestion, with swelling. They belong to a very definite group of vasomotor disturbances in organic lesions of the brain and cord, and I feel that it is better not to group them with erythromelalgia, however much the features may simulate this disease.

Endarteritis Obliterans.—Pain, redness, and swelling are common symptoms in one or both feet in Friedländer's disease—the progressive sclerosis of the arteries of the legs. It is a common affection, often confounded with erythromelalgia. A woman, aged sixty—about whom the doctor had written suggesting the diagnosis of erythromelalgia—began to have pains in the left leg and foot, and when she walked any distance the foot became swollen and red and the sole was very tender. At rest she was comfortable, although at night the leg was sometimes painful. Then she noticed a peculiar inability to walk more than a certain distance, after which she had to stop quite suddenly and felt as if her legs would give way; after a few minutes' rest she would go on again. When I saw her, five months after the onset of the symptoms, the symptoms of intermittent claudication were present in a typical form. The left leg and foot were swollen and painful, and of a dusky red color, which increased to a purple when the leg hung down.

After rest or if the leg was placed upon a pillow the color became almost normal. No pulse could be felt in the arteries of either leg, both dorsal arteries were sclerotic, and there was general arteriosclerosis. This was a typical case of intermittent claudication and the vasomotor disturbances associated with endarteritis obliterans. The pain may be most severe and persistent, as in a case I give in the chapter on Raynaud's Disease. The color is often less marked than in the case here mentioned, and a preliminary spasm of the vessels may cause ischæmia. The arteries are not always obliterated. As Erb[1] has pointed out, these cases are very common, and while they occur, as a rule, in elderly people, this group of symptoms may be met with in young or middle-aged men, the subject of syphilitic or other forms of endarteritis (Parkes-Weber). Three features distinguish these cases from true erythromelalgia—the presence of arterial changes, the tendency to gangrene, and the occurrence of intermittent claudication. Minor points are the greater liability to asphyxia and the great variability of the pain. There are cases without any disturbance of sensation, particularly in diabetes.

Neuritis.—A "red neuralgia" is often the best description of a local neuritis. I have seen two cases in which a neuritis of the arm caused a condition very similar to erythromelalgia. A woman, aged fifty-six, began to have pain in the left shoulder and limitation of movement, and within a few weeks the joint was immobile, but with very little swelling. Soon the pains began to spread down the arm, and the fingers and hands became red and swollen. The pains were most intense and required morphine for their relief. The swelling and redness extended nearly to the elbow. The course of the chief nerves was painful to the touch, and the skin was everywhere hyperæsthetic. The late Dr. Seguin, of New York, saw the patient and made a diagnosis of arthritis and consecutive neuritis. The patient recovered after more than four months of swelling and redness of the arm, and it was nearly a year before the shoulder-joint could be moved freely. In this type of local arthritis of the shoulder, pains along the course of the nerves are not uncommon, but redness and swelling of the forearm are rare. I saw a second case with Dr. H. M. Thomas. The other condition is pressure on the brachial plexus. In connection with Raynaud's disease, reference was made to cases described as due to tumors pressing upon the cauda equina or the lumbar nerves. In a woman, aged forty-three years, with secondary carcinoma of the supraclavicular and axillary glands, the fingers became numb and painful, then a vivid redness spread over the whole hand, and gradually extended to the middle of the forearm. There was little or no swelling, and no sign of venous obstruction. The pains in the arm, particularly along the inner side, became very intense, and for weeks the picture was that of an acute erythromelalgia. As the tumors increased there was pressure in the veins and great swelling of the arm and hand.

The alcoholic polyneuritis may be associated with marked vasomotor changes, rarely the active hyperæmia, more often an extreme passive congestion, particularly when the limb hangs down. In a number of cases described as erythromelalgia the pain and redness have been in the course of individual nerves, the posterior tibial, the right internal plantar, the median, or the ulnar. It is by no means easy to say in these cases whether an actual

[1] It is a mistake to call intermittent claudication and endarteritis *Erb's disease* as Cassirer does. The condition was well recognized in man and horses years before Erb's admirable paper, which only served to call our attention to its frequency.

neuritis exists, but we know that with inflammation of a nerve very severe pain and redness may occur. A nurse in the fourth week of a severe typhoid fever began to have pains in the front of the left arm, and in a few days there was a definite swelling between the elbow and wrist, with redness extending to the latter and severe pains on movement or when the parts were touched. The fingers were not involved. The post-typhoid neuritis is usually a motor affair without much pain, but occasionally there are marked vasomotor features, redness, swelling, and pain.

Under Raynaud's disease the question of scleroderma has been sufficiently discussed. It would not be possible, I think, to mistake erythema exsudativum multiforme for erythromelalgia, or any of the forms of acroparæsthesia or of podalgia.

There is one painful state of the arm and hand to which I may refer, as it may be associated with a transient erythema. In 1888, at the Philadelphia Neurological Society, I showed a man whose right arm on exertion became painful, hot, and swollen. In all other respects he was healthy. The symptoms had lasted for years. No explanation could be offered except that it was some sort of vasomotor disturbance. A second case, a woman, presented identical symptoms. Again I was puzzled. She had much redness and swelling and the arm became very painful when the exertion was continued. Last year (1908) I found the explanation of these cases which had stood out in my memory so vividly. A very healthy woman, aged about thirty-five years, consulted me for pains in the left arm and hand, swelling on exertion, which if long continued resulted in a flushing of the whole arm and hand. At once I saw a familiar picture. But this time I was wiser. She was stout, and I could not well determine the presence of cervical ribs, but the *x*-ray photographs left no doubt as to the cause of these remarkable symptoms. The pressure of a cervical rib may be either on the nerve cords or on the subclavian artery. The pulse was not altered in this case, but the disability on exertion suggests intermittent claudication, as if the subclavian admitted enough blood with the arm at rest, but extra demands could not be met, and the muscles failed to act for want of blood. The flushing and swelling suggest irritation of nerve cords, but in none of these cases was there atrophy of the muscles of the hand so common in connection with cervical ribs.

Treatment.—An obstinate chronic affection, very resistant to all forms of treatment; such is the universal judgment of writers. It is best to carry out a systematic plan of treatment. Rest of the parts relieves the congestion and allays the pain, but not in all instances, as the redness may disappear without the pain. The rest should be protracted for six weeks or if necessary, three months. Massage, daily if it can be borne, very gently at first and afterward more vigorously. Many patients prefer cold, and some form of hydrotherapy may be tried, either cold packs or douches, or if grateful, a local steam bath. Radiant heat should be given a thorough trial. The procedure suggested by Cushing, mentioned under Raynaud's disease, should prove helpful. Various forms of electrical treatment have been advised, and may be used. Locally and internally the resources of the pharmacopœia may be taxed to the uttermost without much relief. It is best, if possible, to avoid the more powerful narcotics, as morphine. In the local form, where the pain is limited to a single nerve territory, section or excision of part of the nerve may be practised.

CHAPTER XXX.

ACHONDROPLASIA. HYPERTROPHIC PULMONARY OSTEO-ARTHROPATHY. PAGET'S DISEASE. OSTEOGENESIS IMPERFECTA. OSTEOPSATHYROSIS. LEONTIASIS OSSEA. MICROCEPHALUS. FACIAL HEMIATROPHY.

By CHARLES P. EMERSON, M.D.

ACHONDROPLASIA.[1]

Definition.—Achondroplasia is a disease of fetal life, early infancy, and possibly of childhood, which affects especially the long bones of the extremities and the base of the skull. The most marked features are: the shortness of the extremities, especially in their proximal segments; the large head, and the trident-shaped hands.

Terminology.[2]—Among the many names which have been applied to this condition are: Fetal, intra-uterine, congenital, annular (?), and micromelic rickets (Winkler, 1871); micromelia pseudorachitica (Marchand and Kirchberg); fetal and congenital cretinism and cretinoid dyscrasia (Klebs, 1874); fetal chondritis (Urtel, 1873); phocomelia, micromelia (Kassowitz), nanomelia, and pseudochondritis (Schidlowski); osteogenesis imperfecta (?) (Stilling, Hecker, and Bidder); osteopsathyrosis (?); osteosclerosis and osteoporosis congenita (Kundrat); defective endochondrial ossification, chondromalacia, chondromalacia micromelica (Marchand); micromelic chondromalacia (Kirchberg and Marchand, 1889); and chondrodystrophia fetalis (Kaufmann).

Achondroplasia (Parrot, 1878) is, according to the criterion of priority, the correct name, since it is the first term proposed which recognizes this condition as a clinical entity. But this term, which indicates an absence of cartilaginous bone formation, is inaccurate, since cartilaginous bone formation is not absent; it is retarded in the case of the long bones, while the vertebræ and short bones, which also develop from cartilage, are scarcely affected. An objection to most of the above terms is that the disease is certainly not entirely a fetal disorder.

History.—This disease has long been well known to pathologists and obstetricians, which is natural, since the majority of cases are stillborn infants. The first good reports of such infants are those of Romberg,[3]

[1] The writer takes pleasure in acknowledging his indebtedness to Professor Pierre Marie, who interested him, his pupil, in this subject and allowed him to study the cases at Bicêtre (Paris) for the preparation of a monograph on achondroplasia, which is in preparation.

[2] The terms followed by question marks were applied with better reason to other conditions which were at first confused with achondroplasia.

[3] *Berlin Thesis*, 1817.

of M. J. Weber,[1] and of Busch.[2] Especial interest in the condition was first aroused by Virchow (1856 and 1858), who described the disease as "fetal rickets." Winkler, in 1871, evidently agreed that it was a form of rickets, since he gave it the name "rachitis micromelica." Parrot[3] was the first to recognize that this conditon was not a form of rickets or of cretinism, but an independent disease, to which he gave the name "achondroplasia."

During preceding years several adult cases of achondroplasia had been described, *e. g.*, the cases of Charpentier,[4] of Swayne,[5] and that of Parrot; but Marie was the first to give a clear clinical picture of achondroplasia in the adult. Since the appearance of his paper[6] great interest in the subject has arisen, as is shown by the large number of cases which have been described and the zeal with which art galleries have been searched for evidence of its existence in the past. The best complete description is Porak's,[7] while the best pathological study is that of Kaufmann (1892).

Achondroplasia in Art and History.—Of all dwarfs, only those with achondroplasia and rickets could fill the position of court dwarfs so popular until the end of the seventeenth and again in the eighteenth century, and serve as the friends and buffoons of kings and queens. That achondroplasics would be well fitted for this is seen by the number now found on the vaudeville stage. They are quick-witted, very active, and good acrobats.

Some of the gladiators who fought before the Roman Emperor Domitian were probably achondroplasic dwarfs. It is stated that the Roman Emperor Caracalla was such a dwarf, but we find no evidence for this.

The diagnosis from art is not easy, since the artist seldom pictures the fine points necessary for a certain diagnosis. In a doubtful case it would be difficult to distinguish between a myxœdematous and an achondroplasic dwarf. The truly infantile type of dwarf seems popular in art. By this we mean a relatively large trunk, large head, and short extremities. In studying in various museums, especially the British Museum, the crude wood and stone images from a variety of barbaric tribes, we were surprised at the number which were micromelic. But what was the writer's surprise to see, during a Christmas season, in one of Boston's largest department stores, a fine display of expensive china dolls, which certainly were good models of cases of achondroplasia. They had relatively large heads, bulging foreheads, limbs relatively short, and even cubical hands.

Evidence of achondroplasia can be found in very ancient art. The pictures on the coffins of certain mummies were probably portraits of the body within. Some of these suggest that these mummies were achondroplasic dwarfs. The Egyptian god Bes, who presided over art, music, the dance, and childbirth, was, some say, achondroplasic, others say myxœdematous (Regnault).[8] The god of Memphis, Phtah, supposed to have formed the world, seems almost characteristically achondroplasic. Parrot[9] first called attention to this, and suggested that the artist gave him the fetal figure, since he was the god of Death. Cestan pronounces this god merely infantile. Many of the statuettes of little athletes, and of all the pigmies from Greece and

[1] *Siebold's Jour. f. Gebürtshilfe, Frauenzim. u. Kinderh.*, 1829, ix, 292.
[2] *Neue Zeitsch. f. Gebürtskunde*, 1836, iv, 110.
[3] *Soc. d'Anthrop.*, 1878, p. 280.
[4] *Arch. de Tocologie*, 1876, iii, 45.
[5] *Transactions of the Obstetrical Society*, 1864, v, 84.
[6] *Presse méd.*, 1900.
[7] *Nouvel. arch. d'obst. et de gyn.*, 1889.
[8] *La Corresp. méd.*, 1900.
[9] *Soc. d'Anthrop.*, 1878, p. 280.

Egypt, probably represent achondroplasic dwarfs. In more recent art Velasquez's "Sebastien de Morra" and "El Primo," and some of the dwarfs in the pictures of P. de Veronese and Julio Romano, are almost certainly achondroplasic.[1] Such a drawf was painted by Cornelius Galle de Vieux. Even Raphael painted such a figure in the foreground of "The Miraculous Apparition of the Cross to Constantine." We may judge that Valerio Cioli, Owen Farrel (1742, 1.37 cm. tall), Wybrand Lolkes (1890, 65 cm. tall), also were achondroplasic dwarfs.[2] It is thought that Barbe de Brandebourg, Simon Paap, and Tom Thumb were myxœdematous dwarfs, and that Balthazar qui de Quatrefages was a microphalic dwarf.

Etiology.—Heredity.—The question of the possibility of inheritance of achondroplasia is interesting, not only for its own sake, but because of the bearing it may have on the origin of certain races of dwarfs and of certain varieties of animals, granting that animals do have this disease. Since the achondroplasic mothers who have had live infants were in nearly all cases on record delivered by Cesarean section, it is hard to believe that certain races of dwarfs can have originated from a few cases of achondroplasia as we know it, and the condition become fixed by inheritance. It is of interest that certain queens (Catharine de Medici, Natalie, sister of Peter I, and others) tried to raise a race of dwarfs by arranging the marriage of such unfortunates, and failed (Geoffroy St. Hilaire[3]). It is also worthy of mention that there are no white races of dwarfs, and that all white dwarfs are evidently pathological. (Among the races of dwarfs are the Akkas and other tribes of Central and Southern Africa, the Mincopies of the Andaman Islands, the Semangs of Malacca, and the Ætas of the Philippines.)

That achondroplasia can be directly inherited there can now be no doubt. Marie accepted three cases as certain (Porak's, Baldwin's, and Boeckh's). In the *Australasian Medical Gazette*, 1907, vol. xxvi, p. 624, is a good report of an achondroplasic mother and child. One of the most interesting cases on record is reported by Porter.[4] The father, aged eighty years, and his two sons were achondroplasics. Also the father and a brother of this octogenarian were said to be achondroplasics. This would mean six cases in three generations. The mothers of these patients were all normal women. There were no sisters in these generations. In addition to the above well-observed cases many other achondroplasia patients have claimed that there were similar dwarfs in their families. Comby[5] reported a boy and his maternal grandfather who were achondroplasics and Poncet[6] a brother, sister, father, and grandfather. It is to be observed that in one such case it turned out on investigation that the father, said to resemble the patient, was not achondroplasic.

Achondroplasia is also a family disease (more than one case in the same generation). A good illustration is the family reported by Porter and the brother and sister reported by Lannois.[7] Chavigny's[8] patient said he was the tallest of four children, all shaped like himself.

[1] Regnault, *Arch. gén. de méd.*, 1902; Meige, *Nouvel. Iconog. de la Salpêtrière*, 1901, xiv, 371.
[2] See Woods and Hewlett, *Intercol. Medical Journal*, August 20, 1902.
[3] *Hist. des Anomalies*, 1832, i, 140.
[4] *British Medical Journal*, 1907, i, 12.
[5] *Bull. de la Soc. des Hôp. de Paris*, 1902, p. 551. [6] *Lyon méd.*, 1902, c, 202.
[7] *Lyon méd.*, 1902, p. 895; Poncet and Peloquin.
[8] *Bull. de la Soc. méd. des Hôp. de Lyon*, April 30, 1903, p. 151.

Nature.—One of the first opinions expressed concerning achondroplasia is that of Virchow, who reported one such case as a "fetal cretin." Even now this case is referred to under this heading. Fortunately the infant is still a museum specimen, and has been since then carefully studied (Klebs[1]). There can be no doubt of this infant being a case of achondroplasia. The next step was made by H. Müller (1860), who identified this condition with rickets. The ordinary rickets, he said, develops after birth; this form runs its whole course *in utero*. Parrot, in 1878, recognized that it could not be identified with the ordinary form of rickets, and named it "achondroplasia." He considered it a dystrophy of the cartilage concerned in the first skeleton formation during the period from the third to the sixth month of fetal life. Kaufmann, in 1892, as a result of the pathological study of thirteen cases, gave it the name "chondrodystrophia fetalis." He pictured the process as follows: For a while the skeleton formation is normal and the bones attain some length. Then the cartilage dystrophy begins. The epiphyseal cartilage activity, instead of limiting itself to one line of growth, becomes sluggish or proceeds in all directions, and adds little to the length of the bones. The marrow spaces invade the cartilage, and also the cortex of the shaft, producing a certain amount of osteoporosis interna. The periosteal bone formation is normal or even unusually active, but has abnormally active bone absorption with which to contend. The vascularity of the marrow and of the epiphyseal cartilage is remarkable, and this, some think, is the cause of the disease. The sclerosis of the cartilage is perhaps a compensatory process on the part of the periosteum and perichondrium to compensate for the softness of this tissue. The ingrowth of perichondrium is an important cause of the cessation of growth and of the bending of the bones. Eberth and Strop explained this strip of connective tissue an infolding of the perichondrium, but Urtel, Hoess, and Kaufmann consider it an ingrowth.

Symington and Thomson[2] described achondroplasia as an arrest, or perversion, of the normal processes of endochondrial ossification of the most definite and universal character, involving, during intra-uterine life, every element of the skeleton. Durante[3] described the process as a sclerosis of the zone of endochondrial ossification. Marie holds that the dystrophy of cartilage is an effect and not the cause, and that the disease is a general dystrophy comparable to myxœdema. What the glandular organ is which is at fault he does not know, but is sure it is not the thyroid gland. It is claimed that achondroplasia is the result of a maternal intoxication or a fetal autointoxication. Durante[4] reported one patient whose mother was luetic, and another whose mother died of liver and renal trouble. He reports also[5] a patient whose mother died of tuberculosis during the pregnancy. Peloquin believed it due to a maternal infection. Cestan claimed that the disease originates *in utero* before glandular activity begins, and so cannot be due to any defective internal secretion. He believes it toxic in origin and akin to rickets. From the appearance of the vessels which are so numerous in the cartilage, it would seem as if the trouble were due to a toxin which

[1] *Arch. f. Exp. Path.*, 1874, Band ii, 70.
[2] *Laboratory Reports of Royal College of Physicians*, 1892, iv, 238.
[3] *Rev. méd. de la Suisse romande*, 1902, p. 809.
[4] *Bull. de la Soc. Anat.*, 1900, p. 785.
[5] *Rev. méd. de la Suisse romande*, 1902, p. 809.

diffuses from the vessels and injures the cartilage (Kassowitz[1]). Of course, some cases have been ascribed to "maternal shock during pregnancy" (*e. g.*, Wood and Hewlett, "a scare;" Varglas, "abuse"). One patient was the son of parents who were first cousins. Basch, in 1896, suggested that the thymus was to blame; de Buck said the condition was one of "degeneration."

Achondroplasia and Rickets.—It will be granted at once that until the pathology of a disease, and especially its etiology, is fairly well understood its relationship to other diseases cannot be profitably discussed. Since the nature of neither rickets nor achondroplasia is understood, we are in no position to say whether or not they are related. They may be different manifestations of one and the same disease. They surely are no more different than various manifestations of tuberculosis, for instance. The only question we can discuss here is, Do the two diseases resemble each other clinically and morphologically? and the almost universal answer is that they do not sufficiently to justify the term "fetal rickets." It should be remembered that for a long time all conditions producing multiple lesions of the skeleton were "rickets," and that from this heterogeneous group many of the bone diseases have been separated. A pertinent question is, Is there a fetal form of the ordinary rickets? If the cases which now pass as fetal rickets and which are not achondroplasia are rickets, then there is. Another question is, Is there a postnatal form of achondroplasia, and does it resemble common rickets? There surely is, and it does not. In both rickets and achondroplasia the cartilages are abnormally vascular, but the vessels differ in size, structure, and arrangement. In rickets there is luxurious cartilaginous formation. The columns of swollen cartilage cells are abundant, and extend in all directions. In achondroplasia they are scanty, and (differing from rickets) the ground substance of the cartilage is nowhere normal but fibrillar or glassy. In postnatal rickets there is very little real shortening of the bones. The limbs are short because the bones are bent. In rickets the bends are pathological, asymmetrical, and bizarre, while in achondroplasia they are symmetrical, and are exaggerations of the physiological curves. In rickets there is relatively more involvement of the bones of the thorax, pelvis, and spinal column than in achondroplasia, although it is now granted that in the latter disease these bones may be slightly affected. There is a rosary in both cases, but careful examination of the bones shows the marked difference that in rickets the swelling is cartilaginous, in achondroplasia it is bony. In rickets the shape of the head is quite different from that in achondroplasia, although we have seen an achondroplasic person with typically rickety head. But we have contrasted above achondroplasia and common rickets, and have brought forward no evidence against the possibility that the two conditions are different forms of one and the same disease. Even since the first it has been granted that typical achondroplasics do show signs of rickets (*e. g.*, the high forehead, with prominent frontal bosses, Harrison's groove, and some bizarre bends of the long bones). Marie admits their simultaneous occurrence. Macewen[2] emphasizes the occurrence of both diseases in children of the same family.

Intra-uterine Rickets.—The tendency is to deny absolutely the existence of this disease. Some insist that it does occur, but that it can be easily differ-

[1] *Wien. med. Woch.*, 1902. p. 1358.
[2] *British Medical Journal*, 1907. ii. 1646

entiated from achondroplasia. It is described as a disease beginning in the second half of pregnancy and in full bloom at birth, the lesions of which are isolated and circumscribed, consisting of bony softening and tumefaction, and which produce asymmetrical curves. The ribs are always affected. The result does not much resemble achondroplasia. Winkler, Urtel,[1] Englisch, Fischer, Borntrager, Smith,[2] and Rumpe have described cases under this title, but the better the description the more certain are we that the condition is achondroplasia. The earlier writers (Winkler,[3] Urtel) separated fetal rickets, which runs its entire course *in utero*, from congenital rickets, which is florid at birth, and from common rickets, which begins after birth. But Urtel did not believe them to be the same disease. Unruh claimed that all rickets is a congenital affection. Kassowitz found evidence of rickets in over one-half of newborn infants, and Feyerabend in 69 per cent. of 108 newborn infants. But Fédé and Finizo could find unmistakable evidence of rickets in but 3 of 475 cases, and Tschistowitch in none of 100 skeletons of children who died at birth (Morse[4]). Simmonds[5] said that he had long been on the lookout for, but had never seen, a case of fetal rickets. Barlow[6] insisted that achondroplasia was not rickets. Porak, Durante, Cestan, and others believe that there is some relationship between these two conditions.

Fetal Cretinism.—Following the opinion of Virchow, many patients have been treated by large doses of thyroid extract. Since there was no improvement we may be sure the condition is not hypothyroidism. But this does not, in the opinion of Cavazzani, clear the thyroid gland of all blame. He[7] reported a case which he thinks unique. The mother had exophthalmic goitre, and during pregnancy she took large and finally toxic doses of thyroid extract. Later the child was given the same drug in large doses. Both showed such a marked tolerance to this extract that he suspects the thyroid gland may in some way be to blame.

Against the thyroid theory it is claimed that in achondroplasia the ossification is rapid and in cretins retarded. But this is not always true. Simmonds stated that there certainly are cases with combined achondroplasia and myxœdema.

Lues.—Several cases of achondroplasia, which were quite surely also luetic, leads one to question if it is possible that achondroplasia is a luetic or paraluetic affection. While the question of the relation to rickets is at present not capable of solution, that of lues is, and in all stillborn achondroplasic infants *Spirochæte pallidum* should be searched for. The question is, Can lues produce a micromelic dwarf? Birrenbach reported the case[8] of a stillborn infant which he says was certainly a case of achondroplasia. But the child was also quite certainly luetic. It had a macerated skin, pemphigus vesicles, white pneumonia, interstitial hepatitis, jaundice, etc. This fetus of eight months was 38 cm. long and its trunk 30 cm. long. The total length of the upper extremity was 10 cm.; of the lower, 11.5 cm. The circumference of the head was 32 cm. Sections of the tibia and humerus

[1] *Halle Thesis*, 1873.
[2] *Inaug. Diss.*, Zurich, 1880.
[3] *Arch. f. Gyn.*, 1871.
[4] *Archives of Pediatrics*, August, 1902.
[5] *Biol. Abth. des ärztl. Verein*, June 18, 1901.
[6] *Transactions of Pathological Society*, London, 1881, vol. xxxii.
[7] *La péd. prat.*, Lille, 1907, v, 125
[8] *Thesis*, Griefswald, 1901.

at the epiphyseal cartilage showed an absence of proliferation of the cartilage cells, which were scattered far apart, and an ingrowth of connective tissue between the cartilage and bone. That is, there was a cessation of cartilage bone formation with sclerosis of the epiphyseal cartilage, while the periosteal bone formation was normal. The rosary was due to the projection of bone over the end of the cartilage. This author likens the fibrous tissue formation to a luetic process, but does not consider this case of micromelia due to lues. Daniel[1] reported a seven and one-half months' fetus with micromelia and rhizomelia, which was the child of a luetic mother. This infant's skull was little ossified, the head burst during delivery, and showed an involvement of the membranous bones, suggesting hereditary claviculocranial dysostosis. There was a fracture of the humerus. The placenta was luetic. He thinks this child was a case of achondroplasia. Durante[2] reported a case, the child of a luetic mother. And this may have been true of Schildowsky's case.[3] Of course, the above relation to lues may have been accidental, but it is natural to associate the conditions in these cases until the contrary is proved.

Gigantism.—The question of a possible relationship between achondroplasia and gigantism has been raised by Lannois. He reported the case of an achondroplasic man, aged twenty-five years, whose next older brother measured 192 cm., while two other brothers were very tall. The father measured only 160 cm. Since the interval between the births of the giant and the dwarf was very short, Lannois suspects some dyscrasia on the part of the mother. Lunn[4] reported a case of achondroplasia in a patient whose father measured six feet two inches in heighs, his mother five feet ten inches, and whose three brothers and one sister were normal. Claudius (Marie's case) came of a tall family.

The numerous cases of achondroplasia which have occurred in large families should call attention to a possible relationship between numerous pregnancies, especially when these occur at short intervals, and this condition. Herrmann's case was one of nine children. Wood and Hewlett reported a case which was the thirteenth of sixteen children, all the rest being normal. Méry and Labbé's patient was one of thirteen children.[5]

Congenital dislocation of the hip is sometimes associated with dwarfism, but also there is evidence that it is in not a few cases associated with achondroplasia. Such cases have been reported by Kassowitz, Kirchberg, Simmonds, and Kaufmann. Patek[6] reported the case of a man, aged forty-eight years, and only 108 cm. tall, with fairly normal proportions, in whom skiagraphs showed double congenital dislocation of the hips. Mouchet[7] reported the case of a man, aged forty-six years, with double congenital dislocation of the hips. This man had also bilateral dislocation of the heads of the radii and of the inferior extremities of the ulnar bones, with partial dislocation of the sternal end of the right clavicle. Kassowitz points out that both conditions are more common in females. while Grawitz[8] claimed that

[1] *Ann. de Gyn. et d'Obstet.*, January, 1903.
[2] *Bull. de la Soc. Anat.*, 1900, p. 785.
[3] *Thesis*, Berlin, 1885.
[4] *Transactions Clinical Society*, London, xl, 252.
[5] *Bull. et mém. de la Soc. méd. des Hôp. de Paris*, 1902, p. 543.
[6] *Gaz. hebd. d. méd et de Chir.*, March 31, 1901.
[7] *Ibid.*, March 9, 1902.
[8] *Virchow's Arch.*, 1885, c, 256.

congenital dislocation of the hip was due to achondroplasia limited to the pelvic bones, the lack of proliferation of the cartilage explaining the shallowness of the cotyloid cavities.

Pathological Anatomy.—Achondroplasia of the Stillborn.—For some unknown reason the great majority of achondroplasic fetuses die *in utero*, and of those which do come to term the majority die soon after birth. These infants attract attention at once, because of their very short limbs, their large heads, and the normal or even large size of their trunks. The umbilicus may be at the juncture of the middle and lower thirds of the total body length. The chest is broad and the abdomen prominent. The nose is broad and flat and its root depressed. The fat cheeks almost close the eyes. The tongue often projects from the mouth. But most noticeable are the short, often fin-like limbs, which give them the appearance of a "marine mammal," a "cetacean," more than of a man (Otto, 1816). The shortness of the limbs is due to abbreviation of both distal and proximal segments, but especially of the latter. This was first noted by Tripier.[1] These infants are plump, since there is usually an abnormal amount of subcutaneous fat. The skin hangs in folds, giving the child the appearance of a "dwarf in much too large clothes" (M. J. Weber, 1829). The genitalia are well developed.

The chief lesions of achondroplasia are in the skeleton, and would seem secondary to disease of the epiphyseal cartilages of the long bones. The subperiosteal bone formation seems normal or even abnormally active, while that at the epiphyses is deficient. The result is thick and strong but short bones. Achondroplasia may begin at any time before birth. The earlier it begins the shorter are the bones. When late in its appearance they may be of normal length. When the disease begins, the cartilage may soften (the malactic form) or grow "wildly" (the hyperplastic form), or merely grow torpidly (the hypoplastic form) (Kaufmann). The bones most affected are the humerus and femur, next the tibia and ulna, and then the base of the skull. The fibula and radius seem much less affected. These long bones vary in length from about the normal to only one-half their normal length. Their diaphyses are about normal in diameter, but their walls vary somewhat in thickness and hardness, and are sometimes even eburnated. They may have no medullary canal. The smaller and more crooked the bones the harder they are. The normal curves of the bones are usually exaggerated even to right angles. In Lecadre's[2] case the legs were so bowed that the soles of the feet exactly faced each other. The curves are symmetrical; there are no bizarre deformities. The prominences for muscle attachments are hypertrophied. The epiphyses are usually of almost normal size, but sometimes are much swollen and misshapen. Some are mushroom-shaped, and give the bones an hour-glass shape. In many cases they are soft. They always are unusually vascular. Ossification in some cases is very retarded, in others is abnormally advanced, and the epiphyses are often firmly united to the diaphyses.

Those bones which do not pass through a cartilaginous stage in their development grow to normal dimensions. This is true especially of the frontal and parietal bones of the skull. It is often stated that the clavicles, pelvis, and ribs, which belong in that class, develop normally, but this is doubtful.[3] The short bones, the vertebræ, metacarpals, etc., develop from

[1] *Gaz. méd. de Lyon*, 1864, p. 314.
[2] *Paris Thesis*, 1856.
[3] See Regnault, *Bull. de la Soc. Anat.*, 1901.

cartilage and were said to escape the disease; but quite certainly they do not always (if ever), although their involvement seems slight.

The skull is voluminous, suggesting hydrocephalus, with prominent bosses and an especially prominent forehead. In some infants true hydrocephalus was found, in others the unusual thickness of the bones explained in part the size of the head. Two cases (one a seven and a half months' fetus reported by Champetier de Ribes and Constantin-Daniel) whose heads burst during delivery by the Mauriceau method, "without violence," were reported as interesting examples of fragility of the skull. In the case reported by Mary A. Smith,[1] there was no bone in the vertex of the skull. However, the diagnosis in both these cases is doubtful (was lues present?).

The frontal and parietal bones usually develop normally, but not so the base of the skull. At birth the foramen magnum is surrounded by a ring of four separate bones, which normally are not united to form the occipital bone until the sixth year. Provision is thus made for an increase in the diameter of this foramen. In the achondroplasic stillborn infant a premature synostosis of these bones is usually found, and so the funnel-shaped foramen magnum is surrounded by a ring of solid bone, which is incapable of much increase in diameter. The small size of this foramen was noted by Sartorious[2] and by J. E. G. Schütze.[3] Langer[4] claims to be the first to describe these changes in the occipital bone. In his case, a fetus of eight months, the foramen magnum was 10.5 x 8 mm., that is, not one-half the normal size. In one infant (Collmann) the diameter of this foramen was 5 mm. The pressure which this small and solid ring must exert on the growing cord is thought to explain the premature death of these infants.

Again, that portion of the base of the skull formed by the occipital and sphenoid bones, the "os tribasilaris," consists at birth of three pieces, the basilar portion of the occipital bone and the pre- and postsphenoid bones. The synchondrosis intersphenoidalis between the last two bones unites at about the time of birth. But the cartilage uniting the sphenoid and occipital bones is not solid until about the eighteenth or even the twenty-fifth year. "On the existence of this cartilage depends the development of the base of the skull, and therefore of the brain" (Virchow). In the achondroplasic stillborn infant these bones are often firmly united, and the clivus deprived of the possibility of growth in length. This seems to have been noted by Sartorius.[5] The clivus is in these cases abnormally vertical ("kyphosis of the skull"—Virchow). This shortening of the base of the skull, from 7.6 cm., the normal, to 4.6 cm. or even less, explains, according to Virchow, the depressed root of the nose. Kassowitz found that the root of the nose could be depressed also when the tribasal bone was of normal length or even wholly cartilaginous, and thinks that the tissues anterior to the sphenoid bone in part at least explain the profile of the face. But this bone, being cartilaginous, does not indicate necessarily that it is capable of growth. Shattuck[6] described a case in which the bones were not synostosed, but abnormally thick and small.

The ribs show a well-marked rosary, but the prominence is due not as in

[1] *Zürich Thesis*, 1880.
[2] *Leipsic Thesis*, 1826.
[3] *Berlin Thesis*, 1842.
[4] *Zeitsch. d. K. K. Gesellsch. der Aerzte in Wien*, 1861, xvii, Heft 5, p. 72.
[5] *Leipsic Thesis*, 1826.
[6] *Transactions of Pathological Society*, London, 1881, xxxii, 369.

rickets to hypertrophy of the cartilage, but to extension of the bone over the end of the cartilage, which it surrounds, as in a cup. In some cases (Grawitz) the rosary is only apparent, and due to an angular deformity at the costochondral articulation. The rosary is usually much more prominent on the inner than on the outer aspects of the thorax.

The vertebræ are usually reported as normal, and yet this is doubtful. There is sometimes a premature synostosis of the body and arch of the upper cervical vertebræ similar to that of the modified vertebra which surrounds the foramen magnum (the occipital bone) (Breus and Kolisko[1]). The clavicles are usually normal. Shattuck first described premature synostosis of the coracoid process of the scapula. The pelvis is sometimes distorted, massive, and ill-shapen, and the sacrum is tilted forward.

Microscopic examination of the epiphyses shows at once the seat of the trouble. The cartilage is abnormal, both ground substance and cells. The line of ossification, often not grossly visible, is quite straight, but is fine. The zone of cartilage cell proliferation with its columns of proliferating cells is absent. The cells are irregularly distributed, are few and scattered. This aplasia of the zone of cartilaginous ossification is stated to be the characteristic lesion of achondroplasia. The intercellular substance is decidedly abnormal. Near the surface it is transformed to fibrous tissue. The rest, instead of being hyaline, is often mucoid and sometimes fibrillar. This fibrillar structure may be so marked that its network can be easily seen. The cartilage is sometimes riddled with vacuoles. There is sometimes a broad mucoid or gelatinous zone against the diaphysis. So abnormal is this cartilage that Trippier[2] said: "There are no epiphyses. In their place is another tissue, reddish and completely resembling muscle tissue." In other cases the cartilage comes directly against a well-ossified spongiosa, or is separated from it by a thin zone of swollen cells. In some cases the completely calcified laminæ of spongiosa show all the signs of metaplastic ossification of the cartilage. The wonder is that the bones grow as long as they do (Kassowitz). Several (*e. g.*, Salvetti[3]) described the direct metaplasia of cartilage to bone.

But the most interesting histological finding is fibrous tissue from the periosteum invading the epiphyseal cartilage. The amount of the invading tissue varies from a few fibers to a definite membrane, and it seems to push in between diaphysis and epiphysis, and to cut off all possibility of enchondrial bone formation, and hence to inhibit the growth of the bone in length. This fibrous tissue is vascular, and encloses in its meshes islands of cartilage and also fat cells, evidence of its periosteal origin. It is always thinnest in the centre and thicker at the margins. In case this tissue invades from but one side, it seems to check growth on this side only. This may account for many of the angular deformities, and, Kaufmann thinks, many of the so-called fractures. One of the best descriptions of these findings is that of Urtel.[4]

An extreme vascularity of the epiphyseal cartilages is an almost constant feature. The vessels run at right angles from the perichondrium directly into the cartilage, and along their course especially does the fibrous tissue develop.

[1] *Die Path. Beckenformen*, Band i, Th. 1, 1900.
[2] *Gaz. méd. de Lyon*, 1864, p. 314.
[3] *Beitr. z. path. Anat. u. Path.*, 1894, xvi, 29.
[4] *Halle Thesis*, 1873.

The marrow spaces are usually large, and the marrow tissue is very cellular and vascular. Giant cells are numerous and their arrangement would indicate active bone absorption. This probably explains the osteoporosis interna which one often sees. This bone absorption may be sufficient to overtake the active periosteal bone formation and leave the hard cortex so thin that it fractures easily.

Lesions of other tissues are inconstant. In a few cases a mild degree of true internal hydrocephalus was present (Virchow, Collmann). Durante[1] thinks there is no well-marked nervous lesion. The thyroid gland in the majority of cases has been found normal.[2] In a few cases, including the famous one of Virchow and that of Neumann,[3] the thyroid was described as large. Sutton[4] reported a child with the thyroid twice the normal size. Salvetti found it "hypertrophied." Bowlby[5] found it absent. The thymus is large in a few cases. The liver has several times been reported as large.

Otto[6] reported the case of a micromelic "hydrocephalic" infant which, because of its general body form, should probably be classed as achondroplasic. This infant also had an enormous liver, and an abnormally large thyroid and thymus; the adrenals were very large and remarkably round; the intestine was short and the testes undescended. The lungs were not divided into lobes; the kidneys were lobulated, and the spleen resembled a bunch of grapes, having twenty-four almost separate lobes, and in addition there were accessory spleens. This child had synostosed parietal bones, the foramen magnum was small, yet there was no union of the bones surrounding it. There were six fingers on one hand, seven on the other, and supernumerary toes. The fingers were webbed. The palate was cleft; there was an umbilical hernia and cleft ensiform.

Kaufmann[7] attempted to separate the thirteen cases he studied into three groups: the hypoplastic, the malactic, and the hyperplastic groups.

Achondroplasia of Children and Adults.—Our knowledge of the pathology of achondroplasia of children and adults is obtained from the study of skeletons found in museums and of radiographs of the living cases. So far as the writer knows, no child or adult achondroplasic has, since the interest in this subject arose, come to autopsy.

The skull is voluminous. The parietal and frontal bosses are usually prominent. The size of the skull is in some of these cases explained by the thickness of the bones. The foramen magnum is abnormally small. In the three adult skeletons studied by Breus and Kolisko[8] its dimensions were: 1.9 cm. x 2.5 cm., 2.2 x 2.8 cm., and 2.9 x 3.4. These writers suggest that cases of achondroplasia be divided into two groups, according to the presence or absence of the premature synostosis of the bones surrounding this foramen. In some cases the skull seems unaffected. The ribs show a bony rosary. The vertebræ seem affected in severe cases, evidently not at all in the mild ones. The arches and bodies of the upper cervical vertebræ seem to have

[1] *Bull. de la Soc. Anat.*, 1900, p. 785.
[2] See Legry and Regnault, *Compt.-rend. Soc. Biol.*, 1902, p. 567.
[3] *Halle Thesis*, 1881.
[4] *Transactions of the Pathological Society*, London, 1884, xxxv, 464.
[5] *Ibid.*, vol. xxv, p. 450.
[6] *Seltene Beob. z. Anat. Phys. u. Path.*, Breslau, 1816, Heft 1.
[7] *Untersuch. über die sogenann. fetal Rachitis* (Chondrodystrophia fetalis), 1892.
[8] *Die Path. Beckenfomen*, 1900, Band i, Th. 1.

prematurely united, if we may judge by the stenosis of the spinal canal of certain skeletons. The long bones of the extremities are short and thick, the normal curves are exaggerated, and the parts for muscular attachment are prominent and strong.

Studies of radiographs of adults would indicate two distinct groups of cases of achondroplasia—those in which the epiphyseal lines does not disappear and those in which it disappears too early. In the first the ossification in the epiphysis is much retarded (the hypoplastic form, the true achondroplasia of Parrot). In the second, ossification is abnormally advanced, therefore the epiphyseal cartilages are much reduced in thickness (the hyperplastic form). This is the classification of Variot.[1] He calls attention to the fact that the result (short bones) is the same in either case. The epiphyseal lines still persist in some patients even forty-five years old.[2] In Poncet's case, a woman, aged twenty-eight years, there had been complete union. In many cases ossification of the epiphyses is much delayed.[3] The bones of the hands and fingers may also show arrested cartilaginous ossification (Comby).

The humerus is surprisingly short. In ten skeletons, all apparently of adults, the length of the humerus was from 14 to 17 cm., with an average of 15.3 cm. (normal about 27 cm.); the ulna, from 10.7 cm. to 15.8 cm., average 13.2 cm.; the radius, from 8 cm. to 14 cm., average 11.4 cm.; the femur, from 16.5 to 24 cm., average 20.7 cm.; the tibia, from 11.6 to 20 cm., average 16.3 cm.; and the fibula, from 16.2 to 21.2 cm., average 19 cm. The skeleton of the hand measured from 10.3 cm. to 14.5 cm. (normal 20 cm.), and of the foot, from 14.5 cm. to 18 cm. (normal 25 cm.).

The scapula is smaller than normal, especially in its vertical diameter, and its glenoid cavity is apparently too small for the head of the humerus (Cestan). The olecranon would seem to be too large for the olecranon fossa. The tibia and fibula are especially interesting. The tibia is much shortened in this disease, but the fibula is much less if any affected. Since the fibula is "splinted" to the tibia, it must find room for its length by abnormal curves or by extending upward and entering into the formation of the knee-joint, or even by extending higher than the tibia.

Varieties.—One of the first classifications of cases of achondroplasia is that of Kaufmann, which was based on the study of thirteen stillborn infants. His first group was chondrodystrophia fetalis hypoplastica. The five cases which illustrated this form had abnormally short but stout trunks, absolutely large heads, and very short extremities, over which the investment of soft tissues hung in tumor-like folds, as if cut out for larger limbs. The thorax was narrow above, wide below, and the "rosary" very marked. The root of the nose was much depressed. The eyelids and the lips were swollen, and the cheeks thick. The epiphyseal cartilages were firm in consistence, very vascular, but normal in size. His second group was chondrodystrophia fetalis malacica. There were three cases in this group, which differed from the preceding in that the noses were depressed as a whole, and the epiphyseal cartilages were abnormally soft. The third group was

[1] See Comby, *Bull. de la Soc. de Pédiat. de Paris*, 1903, No. 5, p. 173.
[2] Pauly and Teyssier, *Prov. méd.*, 1900, xiv, 409.
[3] See Broca and Debat-Ponsan, *Bull. et mém. de la Soc. de Pédiat.*, 1907, p. 91; also Variot, *Bull. et mém. de la Soc. méd. des Hôp. de Paris*, 1907, xxiv, 128.

chondrodystrophia fetalis hyperplastica. Of this, Kaufmann reported but one example. This case differed from the others in that the mushroom-shaped epiphyses caused a swelling of joints, as in rickets. The bones were hard, and seemed disposed to fracture, since five long bones showed fresh breaks. The hypertrophied cartilaginous epiphyses were fairly soft and quite vascular. The trunk of this infant was unusually long (42 cm.). The growth of the cartilage is described as "wild." Kaufmann believes this to be the only case of the variety reported. He admitted that four of the thirteen cases did not belong in any one of these groups. Regnault[1] says that these three varieties are only grades, of which the hypoplastic variety alone is viable.

The study of radiographs of living cases led Variot[2] to separate a hypoplastic and a hyperplastic form. As an illustration of the hypoplastic variety, he reports the case of a girl, aged thirteen years, in whom ossification was much retarded. The head of the humerus seemed crushed, and the lower end of this bone was cartilaginous for 1 or 2 cm. above the joint; the lower ends of the radius and ulna were little ossified, while the carpals and especially the metacarpals were almost as cartilaginous as at birth. The same, but in lesser measure, was true of the bones of the lower extremities. Variot compares this case with that of Méry and R. Labbé,[3] which he considers an illustration of the hyperplastic form. This was a boy, aged twelve years, in whom ossification was abnormally advanced and the epiphyseal lines early obliterated. Since the head in the case mentioned above (the girl aged thirteen years) was unaffected, while all the other signs of achondroplasia were present, Variot proposes to call such cases "achrondroplasia without cranial involvement" or "epiphyseal dyscrasia."

The above may be one illustration of a "partial" case. Pauly and Teyssier[4] reported the case of a man, 138 cm. in height, who lacked the head changes, the trident hand, and the relatively long fibulæ; Chavigny[5] reported the case of a man, 151 cm. tall, who would seem to be of a very mild type. Regnault also is confident that partial forms do occur.

Achondroplasia is accompanied by many other deformities and abnormalities. Among these are hypospadias, cervical cysts, spina bifida, arrested development of the ears, arrested development of the ensiform cartilage, umbilical or inguinal hernia, cleft palate, genu valgum, and a large variety of tumors.

It is claimed that achondroplasia occurs in animals also. The cases which resemble it most are the rare "bull-dog calves," first mentioned by Daubenton in 1750. These calves have very short snouts, short legs, thick, wrinkled skin, and yet normal developments of the short bones. These cases were collected by Peloquin. But the greatest interest is in the question whether or not certain well-defined species of animals are illustrations of achondroplasia fixed by inheritance, and that the condition is therefore normal for these animals. These animals have short legs or short snouts, or both (the dachshund, the pug dog, guinea-pigs, Ancon sheep, the Nato's cows of Chili, Yorkshire pigs, etc.). There has recently been a rather warm

[1] *Arch. gén. de méd.*, February, 1902.
[2] *Bull. de la Soc. Pédiat. de Paris*, 1903, No. 4, p. 150, and No. 5, p. 173.
[3] *Bull. et mém. de la Soc. méd. des Hôp. de Paris*, 1902, p. 543.
[4] *Prov. méd.*, vol. xiv, p. 489.
[5] *Bull. de la Soc. méd. des Hôp. de Lyon*, April 30, 1903, p. 151.

discussion on this point between Leblanc,[1] who wished to associate these conditions with disease of the thyroid gland, Apert,[2] and Regnault.[3] The opinion seems to hold that if any condition in animals is comparable to achondroplasia in man, it is that of the "bull-dog calves," and that the body form of the above-mentioned races of animals is the result of a slower evolution and the similarity to achondroplasia is accidental; yet achondroplasia is a disease which may be inherited.

Symptoms.—While the great majority of achondroplasic infants are still-born or die during the first year, those who do live more than one year seem to have the average chance of life. As the child develops, the seeming disproportion between the amount of loose skin and the length of limb seems to disappear. Teething, talking, and walking, the three events by which an infant's progress is usually measured, seem normal in the majority of those children who are clearly achondroplasic at birth. But some of these infants do seem slow of development.

The appearance of the adult achondroplasic is striking. The most noticeable points in his appearance are the short extremities, the body of almost normal size, and the large head. Achondroplasics are dwarfs in the sense that they are shorter than the normal man. Of eighteen achondroplasic men, all over twenty-one years of age, the heights varied from 93 to 138 cm., averaging 119 cm. Of eighteen women with this condition, all over twenty-one years of age, the heights varied from 97 to 130 cm., averaging 116 cm. The trunks of these patients are usually described as normal, and while this may be the rule, yet in well-marked cases there seems to be a slight microsomia also. The women are usually stout, while the men are very muscular. The legs are short, even but half the normal length. The arms are affected in about an equal degree with the legs. This micromelia is the important sign of achondroplasia, but what is even more important is that the root segments, upper arm and thigh, are relatively shorter than the distal segments; that is, the condition is one of rhizomelia. The upper extremities hang down to about the crest of the ilium, seldom below the greater trochanter. The shoulders are attached slightly more posteriorly than normal. Owing to the small size of the cotyloid cavity, the arms cannot hang vertically but project slightly from the sides (Marie, Poncet). The bones of the arms are only slightly curved. Since the olecranon cavity seems abnormally small, the humerus and ulna are articulated at an angle, and the arm can seldom be extended straighter than 135 degrees. The articular fold of the elbow is more oblique than normal. The radius seems relatively too long, and its head is so large that supination is limited. The hands have a characteristic shape. They are small, short, and thick, and since the fingers are all of about equal length, have a cubical shape. The ring finger seems to lie in a plane posterior to the others, and is almost covered by them. The first phalanges lie parallel, but beyond these some or all of the fingers diverge like the prongs of a trident, giving the hand the "trident shape" described by Marie; but this is not a constant feature. The legs are often bowed or are knock-kneed, due not to curves of bones but to the joints, since the bones are articulated at an angle. The head of the tibia

[1] *Compt.-rend. Soc. Biol.*, 1902, p. 88; *Lyon méd.*, 1902, xcviii, 238.
[2] *Compt.-rend. Soc. Biol.*, 1902, p. 127; *Bull. méd.*, 1902 p. 123.
[3] *Compt.-rend. Soc. Biol.*, 1902, p. 1203; *Bull. Soc. Anat.*, 1901, p. 386.

is large; the marked curves and high position of the fibula are often palpable. The toes are of almost equal length. The joints are abnormally lax, especially the knees, and those of the hands and feet. The spine shows an interesting and quite constant abnormality in that the sacrum tilts forward into the pelvis, with a resulting sharp lumbar lordosis, which explains the contracted pelvis. The thoracic spine is so straight that the back is flat.

The head is usually globular in shape, with well-marked frontal and parietal bosses. The macrocephaly is an important and yet variable feature. Apert reports a patient the circumference of whose head was 66 cm., and Marie a man with a head 67 cm. in circumference. Of eleven men, all over twenty-one years of age, the heads measured in circumference from 54 to 67 cm., averaging 59 cm.; of five women this circumference varied from 52 to 56 cm., averaging 54 cm. Brachycephalia is an almost constant feature, and the cephalic index is usually over 0.9; in one of Marie's patients it was 1. The shape suggests hydrocephalus, and yet the evidence thus far is against this and more in favor of a thick skull (Cestan). A retardation in the closure of the fontanelles and sutures is almost constantly present.

The face is relatively small, but absolutely large. The features are coarse, the forehead prominent, and the eyes deep. The nose is especially characteristic. It is short, its base is broad, its root very deep, and its tip prominent and thick. The nostrils are large. The hard palate is frequently high-arched, but the teeth usually show no abnormality.

In some cases these skull changes may be absent. Variot proposed to separate these cases into the separate group, "achondroplasia without cranial dystrophy." Jaboulay[1] reported one such case. The shape of the head may be asymmetrical (Langenbach[2]).

The adult achondroplasics are remarkably strong, even when compared with normal men. Strange to say, they seem to choose, or at least not to avoid, strenuous work. Porter's[3] patient was a man, aged eighty years, who, until he was seventy years of age, did exceedingly hard work. They are excellent athletes, and popular circus acrobats, not only because of their conspicuous build, but actually because of their strength and skill.

The intellectual development of these patients has attracted considerable attention, and yet we fear the whole class of achondroplasics has been judged by those first accurately reported. They are often described as rather limited mentally, mischievous, intemperate, and lascivious. This may be true of many, but it is not of all. We have in mind several born in good families whose mentality was of the highest order, students and teachers of excellent ability. The child of the lower classes must depend on the public schools for education, and here the achondroplasic child will learn little, since his mates will make his life miserable. Kassowitz states that among his cases there were girls who were unusually bright, notwithstanding their stupid appearance, and Poncet claims brilliancy for one of his patients. De Buck,[4] Villaire Cabeche,[5] Jaboulay, Poncet,[6] Lannois, and others claim normal mental development for their patients. It is interesting that the majority

[1] *Prov. méd.*, February 1, 1902
[2] *Virchow's Arch.*, 1907, clxxxix, 12.
[3] *British Medical Journal*, 1907, i, 12.
[4] *Belgique méd.*, 1900, p. 737
[5] *Paris Thesis*, 1902.
[6] *Lyon méd.*, 1903, c. 202.

of the bright patients are women, and the majority of those intellectually inferior are men. Can this be explained by the better home training the females would naturally receive? It is certain that several of the brilliant individuals whom we know had enjoyed good home instruction. Others were reported as bright when children, but rather inferior when grown to adult life. This would agree with the idea that there is retarded intellectual development at about puberty in some cases (Pauly and Teyssier[1]). Marie called attention to the probable relation between the height of the patient and his intellectual development, a point well illustrated by three adult men in his clinic. Claudius, 107.5 cm. tall, aged twenty years, was a child, behaved as one, was mentally puerile, and physically was evidently not at puberty. Anatole, aged forty-one years, 122 cm. tall, was frolicsome, boastful, mischievous, intemperate, and lascivious. Surgeus, aged sixty-six years, just a little taller, was a jeweller by trade, and a sober, married man.

Mentality may depend in some measure on the stage of the disease. The children born achondroplasic seem to develop as rapidly as do other children, but in those in whom the disease continues or appears after birth there seems to be a retardation of the mental development. Rankin, Mackay, Lunn, and Cranke's[2] patient, a boy, aged nine years, who was achondroplasic at birth, was unusually bright for his age. Poncet's[3] patient, a woman, aged twenty-eight years, a congenital case, when thirteen years old stood second in her class at school and since then had earned her living reading to a blind person. But in Herrmann's[4] patient the condition was not noticed until he was ten months of age. He did not talk until he was seven years old, and after seven years of schooling had not left the primary grade. The above are a few examples. Of course, no rule can be formulated, for mentality depends on too many factors.

Sexually, these patients are well developed both anatomically and functionally. Many patients of both sexes seem unusually salacious. Some men are notoriously so, while unmarried women in the obstetric clinics have given the best opportunities for the study of achondroplasia. Apert mentions a woman with contracted pelvis who underwent operations for three pregnancies.

One of the most interesting subjects connected with this disease is that of its postnatal course. The first cases described were all stillborn children in whom the disease seems to have run its course. The terms "congenital rickets," "chondrodystrophia fetalis," etc., emphasized the belief in the nature of the disease. The authors who reported cases in which the condition was not noticed at birth contented themselves with some observation on the "stupidity of the mother." Some mothers may be stupid, but few are so dense that they would fail to note achondroplasia in an infant not their first. If they did overlook it, the neighbors would very soon enlighten them. So many observations on the postnatal course of achondroplasia have now accumulated that we feel there is no longer reasonable doubt on this point. In most cases the disease may run its entire course and heal *in utero;* that is, at birth there is no evidence of active epiphyseal new-bone formation. These cases are stillborn. In other cases the disease seems still florid at birth,

[1] *Prov. méd.*, 1900, xiv.
[2] *British Medical Journal*, 1907, i, 11.
[3] *Lyon méd.*, 1903, c, 202.
[4] *Archives of Pediatrics*, January, 1903.

while it would seem as if some infants apparently normal at birth developed achondroplasia later.

The clinical symptoms of this disease are so important that we copy a few clinical reports. Kassowitz[1] gave the first good report of such cases. He followed several patients for years after birth and noted accurately the postnatal course of the disease, reporting measurements and publishing photographs, which are very convincing. Swoboda[2] considered that the whole course in his case was postnatal. Both mother and grandmother said that the patient's limbs were of normal length at birth. The child was stout, and her flesh so soft and flabby that they feared to lift her. She had a congenital left genu valgum with flat foot. During the next ten years at least forty medical examinations were made by almost as many physicians. The head began to enlarge after the first year and the child walked at three years. At first there was lumbar kyphosis, which became a lordosis as soon as she began to walk. The muscular system was well developed. The soft, tender flesh and the excessive sweating about the head led to the diagnosis of rickets until she was ten years old, when the diagnosis of achondroplasia was made. Intellectually the girl was normal. Reyher[3] reported a case of achondroplasia which he examined when the child was four months old, and again when it was eight and one-half months of age. During this interval the gain in weight was only 50 grams a week (the weight rose from 4600 to 5660 grams). The total length changed from 51 to 56.5 cm., a gain of only 5.5 cm. instead of at least 11 cm., as normal. The circumference of the head on the first occasion was 40 cm., on the second 42 cm. It is interesting that on the first examination the distance from the crown of the head to the navel was 26 cm., and from the navel to the soles of the feet 25 cm. Four and one-half months later these two figures were 33 cm. (normal at eight and one-half months, 38.5 cm.) and 23.5 cm. (!) (normal, 31.5 cm.) respectively (evidently the legs had become bowed).

In many cases the child suffered during infancy from some acute illness. Woods and Hewlett[4] reported the case of an infant who at twelve months "couldn't hold up its head," and who walked at two years. At seven years of age this child was "normally bright." These authors also reported a child who walked when four years old and one who had "hydrocephalus" when nine months old, and walked and talked when eighteen months old. For years afterward the head sweated profusely at night. This child was "normal mentally." Lannois[5] reported a brother and sister both achondroplasic. Both were normal at birth, and in both cases the achondroplasia was noted at the sixth year. (There is some doubt as to this history; they were reported by Tissié, and also by Peloquin.) Cavazzani[6] studied a case from the third to the sixth year, and is sure the deformity increased. This child was achondroplasic at birth. Lunn's patient[7] "lost for a while the use of the limbs." In Herrmann's case[8] the condition was noted when the child was ten months old. He walked and

[1] *Wien. med. Woch.*, 1902, No. 28, p. 1358.
[2] *Wien. klin. Woch.*, 1903, No. 23, p. 669.
[3] *Char. Ann.*, 1907, xxxi, 129.
[4] *Intercol. Medical Journal*, 1902.
[5] *Lyon méd.*, 1902, p. 895.
[6] *Péd. prat.*, Lille, 1907, v, 125.
[7] *Transactions of the Clinical Society*, London, xl, 252.
[8] *Journal of Pediatrics*, January, 1903.

talked when seven years old. Bernstein[1] reported a case with achondroplasia not noticed at birth. The child had some "acute illness" at ten months, and was "weak" for four years, at the end of which time the achondroplasia was first noticed. Broca and Debat-Ponsan[2] reported the case of a typical achondroplasic, eight years old, who was normal until three years old, at which time her growth stopped. We have had excellent opportunities to study one marked case, an adult man whose parents were by no means poor and ignorant, whose mother has repeatedly told the writer the story of his infancy. There seems no doubt that the child was born with normal proportions, had, as an infant, an acute disease resembling rickets, and that signs of his deformity began at about four years of age.

We may, therefore, believe that achondroplasia is a disease which may develop after birth. Its symptoms are those of an acute disease, which considerably retards the child's normal development. Flabbiness and tenderness of the flesh and sweating of the head are prominent symptoms. The teething, talking, sitting up, and walking are all retarded, and the relative micromelia is first noticed after this illness. But some of these are the classic symptoms of rickets! May it be that true rickets is superimposed on achondroplasia? That is possible, but one is inclined to consider the condition as acute achondroplasia and to leave the relationship between achondroplasia and rickets to the future to settle.

Diagnosis.—The true nature of achondroplasia we do not know. Pathologically, the condition would seem to be a disease of the epiphyseal cartilages, which renders them incapable of much new formation of bones. In the case of the fetus, Durante[3] emphasized the point that the gross appearance was not enough for diagnosis, but that microscopic examination should be made to demonstrate that the brevity of the limbs is due to disturbance in the cartilaginous ossification. In the living patient this is impossible, and the radiographs may show either too little or too much cartilage at the epiphyses.

It will be necessary to state first just what features the case must present to warrant the diagnosis of achondroplasia. Most will agree that these are dwarfism due to micromelia (especially affecting the root segments) and a trunk of almost normal size. But is this clinical picture always due to the same disease, or can several diseases cause it? Dwarfs are of several types. We have those individuals who are small in all dimensions but whose proportions are practically normal. Lancereaux gives the upper limit of height of these as 120 cm. These are "true dwarfs," and in this strict sense the achondroplasic is not a dwarf. Among the other dwarfs are those resulting from disease of the skeleton, especially rickets and achondroplasia, and those due to general disturbances of nutrition. Among these latter are myxœdema and congenital lues.

Infantilism is a term applied to the condition of the body in which the proportions of youth persist in adult age. The growth in height may not be stunted, although it usually is, but the limbs are relatively long, the head is small, and the secondary sexual characteristics do not develop. The infant is not in this sense infantile, for its limbs are relatively short and the

[1] *Cleveland Medical Journal*, vii, 12.
[2] *Bull. de la Soc. de Péd.*, 1907, p. 91.
[3] *Rev. méd. de la Suisse romande*, 1902, p. 809.

head large. The achondroplasic dwarf resembles much more the infant than the youth, but the secondary sex characteristics are developed even abnormally. There is a rule which will be found useful in studying patients for traces of infantilism or achondroplasia. The length of the forearm from the tip of the olecranon to the tip of the middle finger is equal to that of the lower leg from the lower tip of the patella to the sole of the foot, and this distance is approximately twice the height of the head from the level of the vertex to that of the chin.

In studying the achondroplasic patient he should be compared always with a person of the same age, not with a child of the same height. This is important, since Cestan has shown that many of the illustrations cited from art may not be cases of achondroplasia, but of infantilism (in the sense that they resemble an infant).

Lannois mentioned a dwarf with rickets who did not grow between the ages of seven and nineteen years; also a man, 134 cm. tall, and of normal proportions, who did not grow after fourteen years of age. His father was alcoholic and of the same size. Tissié[1] reported the case of a girl, aged twenty-one years, 98 cm. in height, and her brother aged twenty years, 111 cm. in height, both well proportioned and with five normal brothers and sisters. He ascribes this retardation in growth from birth to an intrauterine disturbance in nutrition and to their unwillingness to eat during their first six years of life, that period when growth is normally rapid and "the child is little else than a digestive canal."

Manouvrier[2] reported a dwarf, aged twenty-three years, 97 cm. in height, weight 17 kg., of infantile proportions, whose growth has been very slow since he was four and one-half years old, at which time he had an illness suggesting tuberculous peritonitis. There were no signs of rickets. The author ascribes this extreme retardation of growth to a fall when three years of age. He was a very light eater when young. This patient grew only 4 cm. between the ages of seventeen and twenty-one years. This author cites other cases of extreme retardation of growth, whose slow growth continued late in life. Jeffery Hudson grew over two feet after he was thirty years of age. Borwiloski was twenty-eight inches (71 cm.) when twenty-two years old, but grew even when in extreme old age. Bébé, the dwarf of King Stanislaus of Poland, died when twenty-two years of age, and 90 cm. in height. Manouvrier thinks that such cases are due to faulty nutrition and that the tissues preserve their embryonic properties even to old age.

Infantilism is seen in cases of mitral heart disease. Lannois[3] reports a case of a girl, aged fifteen years, the size of a girl of eight years, whose arrested development was due to adhesive pericarditis. He states that no cardiac dwarf has as yet been reported whose height was under 140 cm. Infantilism is seen also in idiots and in cases of pancreatic disease. But these cases seldom confuse, for their slender trunk, lack of development of the secondary sexual characteristics (hair, etc.), and especially their small head, will distinguish them from the achondroplasics.

The achondroplasic dwarf is a deformed dwarf, and this deformity consists in the brevity of the legs and arms—that is, he is an "ectromelus"

[1] *Gaz. des Hôp. de Toulouse*, 1897.
[2] *Jour. de clin. et de la Thérap. infantiles*, 1897.
[3] *Soc. de anthrop. de Lyon*, 1902.

("aborted limbs," a monster with arrested development of the limbs). He is also a "phocomelus" ("seal limbs," a monster with shortened arms and thighs, with hands and feet attached almost directly to the trunk). The adult rachitic dwarf is short because his legs are so bowed. They may have also an infantile micromelia, but one not nearly of such a degree as has the achondroplasic, nor have they the rhizomelia of this condition. Their arms are relatively long, the diaphyses of the long bones are curved, the thorax is much involved, and the hands are not trident-shaped. Lannois reported two interesting dwarfs, due to rickets; one was a woman, aged thirty-seven years, 124 cm. in height, whose shortness was due to bends in the femurs just above the knees. The myxœdematous dwarf or cretin is distinguished by the infantile condition of the body, trunk, and limbs, his very reduced mental state, his dry and myxœdematous skin, dull facies, etc.

Patel[1] considers that nearly all dwarfs with practically normal proportions and without signs of myxœdema or achondroplasia are cases of acquired athyroidism due to atrophy of the thyroid gland at the age of ten or twelve years. He cites El Primo (dwarf of Philip IV) as of this group. He describes also a dwarf, a man, aged forty-eight years, 108 cm. in height, with double congenital dislocation of the hips. He was well developed sexually.

Prognosis.—The great majority of achondroplasic infants are still-born, having died at the eighth month of intra-uterine life. The reason for their death at just this time in so many cases is not known, but there seems good reason for the view that it is due to pressure on the spinal cord by the small rigid ring of bone formed by the synostosed bones surrounding the foramen magnum. If this be true, then the prognosis will depend on the rapidity of ossification at this point. There certainly is no reason why the premature ossification occurring elsewhere in this disease should menace life. Regnault believed that infants with the hypoplastic form alone might survive. In these cases the cartilaginous bone formation is sluggish. Variot used the terms hypoplastic and hyperplastic in a different sense. He had reference to cases in children and adults. According to him, the hyperplastic form is that with rapid ossification of the epiphyseal cartilages, while cases with the hypoplastic form retain these cartilages even to old age. Among adults the latter form seems the rule, and this may indicate that the prognosis in the former is worse. If we were to apply this reasoning to infants, we might claim that the hyperplastic variety in Kaufmann's sense had the best prognosis, since Kaufmann could find but one case among the dead fetuses, and but few have been reported since. We cannot be sure, however, that these forms occur in equal numbers. It is possible that the pressure on the cord by this rigid ring of bone explains the unusual number of deaths of these infants during the first year. But after the first year achondroplasic patients seem as long-lived as normal persons.

Reviewing all the evidence, we should believe that the death of these fetuses and infants is due to some mechanical cause, and are inclined to regard the rigid foramen magnum as this cause. The conditions which determine the premature synostosis at this point are unknown. Rapidity of bone formation at the epiphyseal cartilages and rapidity of ossification of these cartilages are possibly related, in that the latter occurs after the former

[1] *Gaz. hebd. de méd. et de chir.*, March 31, 1901.

ceases and marks the healing of the cartilage disease. But this can hardly explain the persistence of the epiphyseal lines in adults. The period at which the disease begins seems less important, since viable infants may have very short extremities and dead fetuses those of normal length.

Treatment.—Any treatment for achondroplasia will, of course, help only those patients in whom the disease is florid after birth. For these, careful feeding, massage, passive movement, electricity, and all possible measures to keep up the general nutrition are indicated.

Congenital Osteosclerosis.—Schmidt[1] reported the case of an infant who died thirty hours after birth, with slight thickening of the long bones but considerable thickening of the spongiosa, especially of the vertebræ, base of the skull, sternum, and the ends of the long diaphyses. The hypophysis of this infant weighed 0.28 gram, or twice the normal weight for an infant of this age. There were no signs of lues. Schmidt was sure that the process was not due to marrow changes. He quotes Assmann,[2] who reported such a case, and ascribed it to healed intra-uterine leukæmia. The hypophysis in this case was small but very vascular.

Pseudo-achondroplasia, Periosteal Dysplasic Type.—Gonnet[3] reported a case of "pseudo-achondroplasia of the periosteal dysplasic type." In body form this child resembled an achondroplasic infant, but crepitation of the humeri, femora, and tibiæ could be produced, and the membranous pouch of the skull contained only a few islands of bone.

Trillat[4] reported a similar case with quite typical achondroplasic body form, but with many fractures of the long bones and with no ossification at all of the cranium. This case is reported because of the difficulty presented in making a satisfactory determination of the position of the child by palpation because of the soft head.

Dyschondroplasia.—This is the name Ollier[5] applied to cases with irregularity in the ossification of the bones. The seemingly normal cartilage ossifies abnormally slowly. Radiographs of these cases show transparent areas in the bones, which at first glance might suggest sarcomas.

This condition is seen in children. They are not dwarfs, and if they are micromelic it is not to such a degree as in achondroplasia. They have not the skull changes and seldom the trident hand characteristic of achondroplasia. There may be slight atrophy of the affected limb.[6]

Hyperchondroplasia.—This is a condition with abnormal lengthening and attenuation of the bones, with increase in width of the cartilages of conjugation. Méry and Babouneix[7] reported such a case. Fournier had reported such cases as due to hereditary lues.

[1] *Verh. d. Deut. path. Gesellsch.*, 1907, ii, 288.
[2] *Beit. z. osteoschl. Anämie, Ziegler's Beiträge*, 1907, Band xli.
[3] *Bull. de la Soc. d'Obstet. de Paris*, 1908, xi, 185. [4] *Ibid.*, 183.
[5] *Bull. et mém. de la Soc. de Chir. de Lyon*, 1889–1890, iii, 22; Molin, *Thesis*, Lyon, 1901.
[6] Nové-Josserand, *Gaz. des Hôp. de Toulouse*, 1899, p. 253.
[7] *Soc. Hôp. de Paris*, July 4, 1902.

THE HYPERTROPHIC OSTEOPATHIES.

From this large and very confused group, for all cases of which the term rickets was formerly used, certain forms have been separated as distinct diseases: General hyperostosis (Friedreich, 1868); osteitis deformans (Paget, 1876); acromegaly (Marie, 1885); chronic pulmonary osteo-arthropathy (Marie, 1890).

In 1772 Saucerott reported the first case with a generalized osteo-arthropathy, a man, aged thirty-nine years, with a skeleton practically all the bones of which, and especially those of the skull, face, and limbs, were hypertrophied. The second report was by Friedreich, in 1868, who reported the famous cases of the Hagner brothers.

The above are but a few, but the best defined, of the many diseases which have been described. And yet, relative to the number of cases observed, examples of pure Paget's disease, pure acromegaly, etc., are rather rare. A great many are reported as "mixed" cases, others as separate diseases, yet standing so near one of the above groups that they may properly belong there. But many, perhaps the most, of these cases, so difficult to classify, are reported before the disease has fully developed and lose their peculiar features years after they were reported.

The tendency among most writers is to consider the above diseases as distinct clinical entities, but several French writers insist that they all are one or perhaps two diseases, and that the chief differences lie in the localization of the lesions.[1] It is interesting that the French would simplify the subject still more. Some think that this "disease" is tuberculosis; others, syphilis. They believe, at least, that they all are manifestations of a toxic condition.

Hypertrophic Pulmonary Osteo-arthropathy.—**Synonyms.**—Hypertrophic pulmonary osteo-arthropathy; toxigenic ossifying osteo-periostitis; osteo-arthropathie hypertrophiante pneumique; secondary hypertrophic osteo-arthropathy; clubbed fingers.

Definition.—By these terms one refers to a symmetrical enlargement of the ends of the fingers and toes and of the distal ends of certain long bones, which condition seems to be secondary to diseases of certain organs, especially the lungs.

Historical.—Hippocrates described "clubbed fingers" as a sign of phthisis. Since then "Hippocratic fingers" have been often observed with chronic heart and lung disease. Cases with hypertrophy of the long bones have received a variety of diagnoses. For instance, the famous Hagner brothers, the bones of whose hands and feet were considerably hypertrophied, were reported by Friedreich in 1868 as cases of "hyperostosis of the entire skeleton," by Paget as osteitis deformans, while Marie reported them first as acromegaly, and later was sure they were cases of hypertrophic osteo-arthropathy. Bamberger, in 1889, reported two cases of bronchiectasis, with clubbed fingers and painful thickening of certain long bones. He said clubbed fingers were not rare in bronchiectasis, and were due to hypertrophy and sclerosis of bone. He is the first who pointed out that they were a part

[1] Ball and Alamartine, *Rev. de Chir.*, Paris, 1908, xxviii, 472, and the many references under the above headings.

of general osseous changes. Soon after, Marie[1] described "hypertrophic pulmonary osteo-arthropathy." He reported cases with thickening of the long bones near the joints, with deformity of the fingers and nails, etc. He considered this to be a secondary condition, and seems to have described it especially to separate these cases from acromegaly, in which group they were causing confusion.

Etiology.—Marie considered that this condition was always secondary to other diseases, and inserted the adjective "pulmonary" in the name, because, of the 8 cases he studied, 4 certainly had pulmonary trouble, in 3 cases this relationship was doubtful, and in 1 it evidently did not exist. Wynn[2] in 100 cases collected from the literature found pulmonary trouble in 68. Alexander found that this relationship existed in 77 of a total of 103 cases. These were distributed as follows: bronchiectasis, 25; chronic pulmonary tuberculosis, 15; empyema, 8; malignant disease of the mediastinum or lung, 8; chronic bronchitis, 2; pneumonia and pleurisy, 2; and cases scattered among twelve pulmonary diseases, 17. Only two cases did not show a definite antecedent disease, and one of these was congenital. Below we add four cases from the Johns Hopkins Hospital medical wards. One occurred with empyema, one with bronchiectasis, one with chronic bronchitis and pleurisy, and one with bronchiectasis and pulmonary tuberculosis.

Teleky's classification of the primary diseases in which osteo-arthropathy may develop is as follows (Sternberg): (1) Diseases with purulent or gangrenous processes in the body; tuberculosis with cavity formation, empyema, bronchiectasis, cystopyelonephritis, dysentery, etc. (2) Infectious disease and chronic intoxications; pneumonia, pleurisy, lues, influenza, chronic jaundice, and alcoholism (?). (3) Heart disease, especially congenital forms. (4) Malignant tumors (carcinoma and sarcoma) of the lung or elsewhere. But this author must have included some atypical and doubtful cases in his lists.

Marie pictures the process as follows: that toxins are produced in a focus of infection; that these toxins are absorbed into the circulation and carried through the body. He thinks that the symmetrical localization of the lesions cannot as yet be explained. Alexander, who was very critical in his selection of cases, found that the association of osteo-arthropathy with pulmonary troubles was more marked than others had claimed, and that the diseases in question were those with a septic focus in the chest, especially bronchiectasis. In other cases there was chronic pulmonary congestion and chronic passive congestion of the whole body.

The bacterial intoxication theory may apply to most of the cases, but certainly does not to those complicating congenital heart diseases. It is supposed that cyanosis is the cause of the tissue proliferation in these cases. But there are many cases of extreme and chronic cyanosis in which clubbed fingers do not occur. Shaw[3] claims that his is the only case of hypertrophic osteo-arthropathy associated with congenital heart disease without any pulmonary lesion.

Alexander and Wynn both mention hypertrophic cirrhosis of the liver as

[1] *Rev. de méd.*, 1890, x, 1.
[2] *Birmingham Medical Review*, 1904, lv, p. 212.
[3] *Clinical Society Transactions*, 1907, xl, p. 259.

a cause of this condition, and Wynn collected eleven such cases. Alexander suggests that here also a chronic toxæmia, bacterial or metabolic, is the exciting factor. Some have considered that hypertrophic osteo-arthropathy may be due to syphilis. The neuropathic theory also has many adherents, and in favor of this are the cases with paræsthesias, those with sensory changes suggesting syringomyelia, one with epileptiform attacks, and those with marked sweating. That clubbing of the fingers may follow a traumatic neuritis is granted, as in Moebius' case of neuritis of the ulnar nerve, with extreme clubbing of the two fingers which that nerve supplies. This patient had tuberculosis also. But in chronic hypertrophic pulmonary osteo-arthropathy the trophic changes in the skin which so often occur in neuritis are not mentioned. In hypertrophic osteo-arthropathy there is as yet no evidence of anatomical lesion of the nervous system. Clubbing of the fingers of one hand has been reported in cases of subclavian aneurism, and in these it certainly is due to passive congestion. One patient had an aneurism of the left subclavian artery with clubbing of the fingers, swelling most marked at the distal end of the forearm and less in the upper arm of the left side. The author,[1] however, denies that congestion alone could cause this and thinks the pressure of the aneurism on the nerve trunks caused a severe neuritis and the hypertrophy resulted from this.

The tuberculosis theory is just now attracting attention. Thorburn advocated this in 1893.[2] Poncet and his pupils have written much on this subject. He considers it benign tuberculous rheumatism. Alamartine[3] says that the correct term for Marie's form of hypertrophic osteo-arthritis is subacute infectious osteo-arthritis, and that the infection is tuberculosis. Ball and Alamartine[4] fortify this opinion with the study of a tuberculous dog with diffuse osteoperiostitis, which they claim is identical with Marie's disease. If we understand these men rightly, they do not claim that Marie's syndrome is tuberculosis of the periosteum or bone. They admit that none of the specific lesions of tuberculosis have been found in the involved bones. They consider it a benign process which develops in a case of tuberculosis. If they believe it to be caused by toxins from a tuberculous focus, then they agree with Marie. Trauma is said to predispose the bone to this condition.

Many others say that the cases without a discoverable primary disease belong to a group by themselves (cases of Gourand-Marie, Gerhardt, van der Weijde-Burnigh, Boeckondt). The congenital cases might be grouped with these.

Sternberg concludes that since the etiology is so varied, one must suspect that the cases diagnosed as chronic hypertrophic pulmonary osteo-arthropathy are not all the same, and that it is a question whether the clubbed fingers and the periosteal changes in the long bones are related. But he calls attention to the fact that while we do see clubbed fingers without periosteal changes in long bones, we do not see the reverse.

Race.—It is interesting that all but 3 of the 117 cases were of the white races.

Sex.—Of the 77 carefully selected cases collected by Alexander, 64 were men and 13 women. Landis said that males are eight times as frequently affected as females.

[1] *Berl. klin. Wochenschr.*, 1903, 75.
[2] *British Medical Journal*, 1893, i, 1155.
[3] *Rev. de Chir.*, 1907, xxxv, 992.
[4] *Ibid.*, 1908, xxxviii, 472.

Age.—While all ages are affected, in the majority of cases the onset is in the third and fourth decade. In a few cases the condition seemed congenital. In one of Marie's cases the condition was noted at infancy, while in another case it seemed inherited.

We know nothing of the conditions determining the disease. Bronchiectasis or chronic pulmonary tuberculosis may continue for years, and then suddenly the hypertrophic osteo-arthropathy appears.

Pathological Anatomy.—There are reports of but sixteen complete autopsies with bone examinations. These are well reviewed by Alexander.[1] Chronic hypertrophic pulmonary osteo-arthropathy is a secondary condition, and its lesions must be carefully separated from those of the primary trouble. Its characteristic lesion is a symmetrical deposit of new subperiosteal bone on the shafts of the long bones. The bones most frequently affected are the lower ends of the radius and ulna, the metacarpals, and the first two rows of phalanges. More rarely the lower end of the humerus and the upper ends of the radius and ulna are involved. In the forearm the new bone begins abruptly as a thin layer, about four or five inches above the wrist-joint, and forms a sheath covering the lower ends of the ulna and radius as far as the epiphyseal line. The circumference of the shaft is about equally affected. The layer of new bone is generally thickest at the juncture of the shaft with the lower extremity of the bone. In Landis' case there was an osteophyte growing from the olecranon. The carpal bones are not affected, but the shafts of the metacarpals are ensheathed and so appear to be uniformly enlarged. The same is true of the first and second rows of the phalanges, but the change is less marked than on the metacarpals. The terminal phalanges are apparently unaffected. Formerly very slight periosteal changes with cellular infiltration and slight periosteal ossification at their ends were described. Changes in the phalanges are hard to judge, since these bones vary so much normally. The corresponding bones of the lower limb, the lower ends of the tibia and fibula especially, are affected. The deposit of new bone on these bones is more diffuse, and may extend over the whole shaft, covering also their upper ends. The layer of new bone is thicker on the tibia than elsewhere, and may be a quarter of an inch thick. Sometimes the lower end of the femur and more rarely the upper ends of the tibia and fibula are also covered. The tarsal bones are not affected. The metatarsal bones show changes similar to those of the metacarpals, but the phalanges of the toes are less frequently affected than of the fingers. Deposits of new bone have been found on the clavicles, iliac crests, and the patellæ. The symmetrical arrangement of the lesions is remarkable.

The cortex of the bone may show some sclerosis and thickening, with diminution in the size of the medullary cavity. The marrow is said to be embryonic in character, with a tendency to fatty degeneration in its central part (Wynn). In one case at least the cortex of the shafts was softer than normal (Alexander). The periosteum is thick and abnormally vascular over the new bone. The main nutrient canals are large, and many additional vessels enter the compact layer.

These bone changes are due to a chronic inflammation, which leads to

[1] *St. Bartholomew's Hospital Reports*, 1906, xlii, 41; see also Sternberg, *Nothnagel's System*, 1903, Band vii, Part 2.

new bone formation, also to atrophy and rarefaction of bone and, to a much less degree, to osteophyte building. The extent and severity of this inflammation vary enormously. The mildest cases show slight ossifying periostitis of certain bones. In severe cases there is a marked affection of the whole skeleton. In severe cases there is extensive osteophyte building. The long bones do not bend. The skull is little if any affected. Marie reported one case with marked thickening of the upper jaw, but no similar case has since been reported.

The bone changes are only part, and often a small part, of the process. There is much thickening of the connective tissue covering the affected bones, especially in the neighborhood of the wrists, ankles, and fingers. The clubbing of the fingers is due entirely to changes in the soft tissues of the finger tips. In many cases an increase of fat alone explains it. Fowler and Godlee say that an overgrowth of the papillæ causes the marked prominence and the mobility of the bases of the nails. Freytag said this is due to the dilatation of the capillary loops in the nail beds. The clubbing disappeared in the finger preserved by Fowler in alcohol, also in the finger which Landis preserved in Kaiserling's fluid. When the *x*-rays were first used the clubbing was supposed to be due to the irregular spicules of bones radiating from the terminal phalanx, but these spicules are not more common or more prominent in the clubbed than in some normal fingers.

In many cases there is excessive fluid in the joints, especially the wrists, knees, ankles, and fingers. In these joints the synovial membrane shows inflammatory changes; it is swollen and gelatinous, the vessels are distended, and the villi show small round-cell infiltration. Thinning, but without loss of polish, of the articular cartilage of the affected joints has been twice described, but, as a rule, there are no cartilaginous changes. There is no lipping, no osteophyte formation, or eburnation of the joints.

The thyroid gland and the pituitary bodies are normal.

Symptoms.—The onset is sometimes with pain, or the patient may notice clumsiness in fine movements, stiffness of the joints, or loss of power as the first symptom. In some cases the acute stage is rather brief, and the condition passes in a few months from its acute to its chronic stage, and develops no farther, although the pulmonary condition which it complicates may progress without improvement.

Thayer,[1] among the first in this country, reported four cases from the Johns Hopkins Hospital Medical clinic. Since then there have been five cases in the clinic, all men.

Case I.—Diagnosis: Empyema, chronic nephritis, and pulmonary hypertrophic osteo-arthropathy. W. S., white, male, aged twenty years, was admitted, complaining of swelling of the legs below the knees. Three and one-half years before admission he had an attack of pneumonia followed by empyema. Thoracostomy was performed just one month after the onset of the pneumonia. Exactly twelve months after this operation this same pleural cavity was opened a second time. At the time of this admission, eighteen months after the second operation, the sinus of this operation was still discharging. He was admitted for swelling of the feet and ankles (œdema due to amyloid degeneration of the kidney?). There was a remarkable grade of clubbing of the fingers, slightly less of the toes. There was slight

[1] *New York Medical Journal*, 1896, lxiii, 33.

thickening of the lower third of the tibiæ and massive thickening of their lower ends, very little of the long bones of the upper extremities, excepting a slight thickening of the lower ends of the radii. He was discharged improved one month later.

Case II.—Diagnosis: Bronchiectasis and hypertrophic pulmonary osteoarthropathy. H. H., aged twenty years on the first admission, was admitted to the Johns Hopkins Hospital sixteen times during a period of ten years, on account of bronchiectasis, with very severe hemorrhages, bronchitis, and pleurisy. The lung trouble began fifteen months before the first admission. The patient said that his mother told him that his hands were abnormally large even when he was a child. He always had difficulty in getting stockings sufficiently large, and always wore large shoes, which he could never lace tightly. For four months before admission the patient had pain in the knees, and for two weeks had been unable to close his hands tightly. Within the last six months he had noticed marked enlargement of the tibiæ, fibulæ, and feet. The patient was sixty-two inches tall, but his frame was not big or remarkably large. The face was symmetrically formed; there was no thickening of the lips, no prognathism, no marked thickening of the upper or lower jaw, and no apparent enlargement of the nose or the superorbital ridges. There was a very marked retraction of the upper part of the right chest, and the right shoulder was considerably lower than the left. One was immediately impressed by the remarkable size of the hands as compared with the rest of the frame. The muscular development of the arms was rather slight, but the hands were extremely large. The lower extremities of the long bones of the forearm, especially on the left side, were quite markedly enlarged, the part above the wrist on the left side standing out rather prominently. The hands, particularly the left, showed interesting changes. The carpal region did not seem to be particularly enlarged. The metacarpal bones, and especially the first on the left hand, were thickened over their entire length, but especially at their distal extremities. The fingers were long and massive. The phalanges felt large, but showed an enlargement by no means proportionate to that of the metacarpal bones. The ends of the terminal phalanges were much enlarged. The fingers were somewhat clubbed, and held in a position of superextension. The finger nails were well formed and smooth, but quite markedly incurved, and resembled the nails of clubbed fingers seen in tuberculosis. The clavicles were normal.

The legs presented a remarkable appearance. The feet were rather large and heavy, but the striking point was the great thickening of the lower thirds of the shins. The tibiæ on either side at their upper extremities were of normal size, but below the junction of the middle and lower thirds they became remarkably large, and at their lower extremities, just above the ankle-joints, the thickening and enlargement were extraordinary. The foot in the tarsal region did not seem to be particularly enlarged. The metatarsal bones did not appear to be as distinctly enlarged as the metacarpal. The toes were somewhat massive and slightly clubbed. The lower ends of the femurs also seemed to be disproportionately thickened.

Careful measurements made on the first admission and again eight years later showed that the condition of the bones had changed very slightly. The circumference of the forearms, 1 cm. above the styloid process of the ulna, increased 5 mm. and 3 mm. respectively; that of the midcarpal regions

5 mm., while the girth of the leg, 8 cm. above the tip of the malleolus, increased 3 mm. on each side. This shows that the condition may at the onset run a rather acute course and then remain stationary, even though the lung condition continues unimproved.

Case III.—Diagnosis: Chronic bronchitis, chronic pleurisy, and hypertrophic pulmonary osteo-arthropathy. W. H. D., white, aged twenty-seven years, had suffered from a chronic cough ever since he was under ten years of age. The pleurisy with which he suffered on admission began acutely seven months before. Two months before admission he noticed, especially when he went up stairs, a stiffness and soreness in the knees, which since then had grown gradually worse. During the last week he noticed that his knees were getting larger, and he thinks that ten days previous to this his hands and feet began to grow larger. Since then they have been tender on pressure, it has hurt him to move them, and he has been unable to close his fists. He thinks that his fingers have always been club-shaped, and says that his father also has clubbed fingers. For the two weeks before admission his hands and legs have been weak. His elbow has been sore and stiff for three days.

On admission his hands and forearms presented a remarkable appearance. The terminal phalanges were clubbed to a remarkable degree. The nails were thin, incurved, and had a parchment-like feel about the roots; they were typical Hippocratic fingers. The skin of the fingers was tight and glossy, and the fingers felt distinctly tender on pressure. The metacarpal bones felt thick and massive, especially toward their distal extremities. The lower third of both radius and ulna showed a remarkable expansion; at the middle of the upper third of the left radius was an indefinite node.

There was a distinct fulness about the lower part of the leg, ankle, and dorsum of the foot, especially at the level of the malleolus. The metatarsal bones felt rather large. There was a general puffy, somewhat œdematous appearance, although no distinct pitting was made out. The second phalanx of each foot looked somewhat Hippocratic. Two years later the cyanosis and the puffiness of the hands were no longer evident. The drawn-tight condition of the skin of the fingers had entirely disappeared. The legs showed still a rather marked enlargement of the lower part of the tibia and fibula, and moderate effusion into both ankle-joints.

Case IV.—Diagnosis: Bronchiectasis, tuberculosis of the elbow, tuberculosis of the lungs, and hypertrophic pulmonary osteo-arthropathy. J. B., colored, aged thirty-eight years, gave a history of pulmonary symptoms for six months before admission. Three months before admission, swelling, pain and stiffness of the feet, ankles, knees, fingers, wrists, and elbows began, also soreness and stiffness in the hips, shoulders, and lumbar spine. There was slight stiffness of the jaws. There were no special changes in the bones of the face. The right humerus, especially its lower half, seemed decidedly thickened and massive. The lower halves of the right radius and ulna were quite markedly thickened and a little sensitive. These osseous changes were less evident in the same bones on the left side. The hands showed very marked changes, perfectly characteristic of those of hypertrophic pulmonary osteo-arthropathy. The metacarpal and phalangeal bones were apparently elongated and thickened, giving the hands the appearance of increase in size and particularly in length. There was marked Hippocratic clubbing of the finger tips, the nails being rounded in the vertical and

horizontal directions. The lower end of the right femur felt slightly thickened, and was sensitive to pressure. The tibia was possibly a trifle enlarged in its lower half. The foot looked large and the toes were a trifle clubbed. Similar changes were present on the left side. The right elbow-joint was decidedly swollen, sensitive, and could not be extended to an angle of more than 165 degrees. There was tenderness, but no swelling of the right wrist. The right knee was swollen, and there was a moderately definite effusion into this joint. The only joint on the left side which seemed affected was the left knee, which was slightly swollen. This patient died during the third admission and eight months after the first admission. Autopsy confirmed the above clinical diagnosis.

Case V.—Diagnosis: Chronic hypertrophic pulmonary osteo-arthropathy. A white male, aged forty-five years, was admitted because of severe abdominal pain. He was a cachectic morphine habitué of the severest type, and died in four days. No autopsy was performed. No past history of his case was obtained. There was thickening of the lower ends of the tibiæ, slight thickening of the radii above the wrist, and slightly clubbed fingers. The percussion note of the base of the right lung behind was high-pitched; the breath sounds were harsh.

Clinical Features.—We follow for the most part Marie's original description (see also Alexander, Thayer, Wynn, and Landis[1]). The hands look enormous, even larger than in acromegaly, but they are not, as in the latter, fairly normal in their general relative proportions, but are deformed and resemble more an animal's paw than the human hand. The fingers especially are affected, particularly the terminal phalanges, and so have the shape of a drumstick. Sometimes the greatest swelling is not terminal, and the finger is spindle-shaped. Marie mentions a patient in whom the terminal phalanx of the middle finger measured in circumference 10 cm. The fingers often seem somewhat longer than normal. Hyperextension of the terminal phalanx has been noted. The joints of the fingers are sometimes swollen and their movements so limited that the fist cannot be completely closed.

The nails are large, even 2.5 cm. broad, and curved both longitudinally and transversely. They may overlay their beds and reach the border of the finger. If the nail was previously long, the end of the finger, when viewed in profile, has the shape of a parrot's head. If previously short, the nail becomes round and fits on the finger like a watch crystal. They often resemble the bowl of a spoon. These nails show marked longitudinal striation, and are brittle and easily split. The root of the nail is elevated and almost fluctuating. In the case of a normal finger the root of the nail is rather firmly fixed to the firm periosteal tissue, and the prominent portion of the dorsum of the nail is on a level with the dorsum of the finger, but at the root there is a sharp cupping. When pressed, the root of the normal nail yields very little. The slightest grade of clubbing of the fingers is evidenced by the increased distance that the root can be depressed on pressure. In more marked cases the dorsum of the nail is in a line with the dorsum of the finger, and the cup at the root disappears. In an extreme case the dorsum of the finger is convex, from the last knuckle to the tip of the nail, and the root of the nail is at the summit of the convexity. In these cases the root of the nail "floats" when pressed and projects as a ridge when the free end of

[1] *Pennsylvania Medical Journal*, 1906–1907, x, 853.

the nail is pressed. This occurs in no other condition (Wynn). The nails grow with abnormal rapidity.

The tips of the fingers are cyanotic, but there is usually a zone of bright rose color at the periphery of the nails. As a rule, all of the fingers are affected, but the thumb and index and middle fingers are often more affected than the other two. Sometimes one or two fingers are alone affected; perhaps those which have received more traumatism than the others. The hand proper is almost normal in size and shape. The forearm above the wrist is so much enlarged that from elbow to wrist it may have a uniform circumference. The ulna and radius at the wrist, especially the latter, project prominently.

Changes similar to those in the hand occur in the feet and ankles, but these are usually less in degree. The malleoli are quite prominent and the great toe is especially affected. Since the lower end of the femur and the whole of the tibia and fibula are enlarged, the knee-joint stands out prominently, and the whole leg may have an elephantine appearance. This hypertrophy may affect the other long bones, especially at their extremities, the humerus and femur, the clavicle, sternum, ribs, and the iliac crests.

The hypertrophy of the bones is often accentuated by atrophy of the surrounding muscles. With improvement in the general condition the swelling may diminish. The lesions of the long bone are usually painful, both spontaneously and on pressure. These spontaneous pains may continue for a long time. In some cases they are persistent, but often they are severe at certain hours, particularly in the evening. In some they are sharp and stabbing and last from a few minutes to half an hour. These pains are increased on motion and on exposure to cold, and are relieved by rest and warmth. They may be so severe that work is impossible. The pains lessen or disappear when the osteosclerosis begins. Certain bones also which are not swollen may be painful on pressure.

In some cases the symptoms of arthritis are conspicuous, but the joints look more involved than they really are. They are swollen and painful and there is increased fluid in the synovial sacs, but they are not red. The joints nearest the affected bones are most involved. The wrists and ankles are the ones most often affected, less often the elbows, the shoulders, and the small joints of the hands and feet. The hips usually escape. The temporomaxillary and sternoclavicular joints are practically never involved.

Apart from the swelling of the bones and joints and the tenderness on pressure, there is clinically no evidence of inflammation. One never sees redness, heat, or suppuration. On movements these joints are only slightly stiff. But even these symptoms are seen only in rapidly developing cases or during an acute exacerbation of an otherwise painless case. It is reported that in some cases complicating bronchiectasis, acute attacks occur which last for two or three days, with pain and swelling of the joints, and that these attacks are coincident with a temporary diminution in the amount of sputum (Alexander).

There is often kyphosis, especially of the lower thoracic spine, but this seems accidental. Atrophy of the muscles of the limbs is sometimes a marked feature, and because of it the swelling of the bones is more conspicuous. This atrophy, however, affects the muscles of the proximal segments and is not symmetrical.

In one case there was a noticeable deformity of the upper jaw. Clubbing

of the tip of the nose has been mentioned. There is often true œdema of the hands and feet. Excessive sweating is a very common feature, and this may be general, or limited to the feet, ankles, and hands. Skin eruptions are common in these cases; among these are ichthyosis, eczema, pigmentation, erythema, excessive growth of hair, etc. The urine is negative.

Clinical Types.—Sternberg separated three types, which may be simply three grades: 1. In the mildest type only clubbing of the fingers occurs. Clubbed fingers are seen in patients with chronic pus-producing diseases of the lung and in those with congenital heart disease. In empyema and acute tuberculous pneumonia the clubbing can develop rapidly, even in a few weeks. After the cure of the empyema by operation the clubbing can disappear almost as suddenly as it developed. As a rule, clubbed fingers are not painful. The attempts to distinguish between simple clubbing of the fingers such as occurs in heart disease and that seen in hypertrophic osteo-arthropathy have thus far been unsuccessful.

2. The second group includes cases with clubbed fingers and also a painful thickening of the long bones, especially those of the forearm and lower legs. This, Bamberger's type, occurs with the same diseases as clubbed fingers, and occurs also in chronic jaundice.

3. The third is "Marie's type," or osteo-arthritis hypertrophica. In the first two groups the lesions are merely incidents in the course of a disease, but in this third group the bone changes are the most important feature and amount to actual deformities. The clubbing of the fingers is at a maximum. The hands are huge, hideous, and "paw-like." The forearms are diffusely thickened. The feet are of giant size, especially the toes and the malleoli. In this form the pelvis, sternum, ribs, and the clavicles are often thickened, and there may be kyphosis of the spine. The symptoms of arthritis are most marked and the patient uses his extremities with difficulty, the gait being painful. In this group the primary diseases may be in the background, or even remain undiscovered. Among them are: Sarcoma of the lung, multiple sarcomas with pleural exudate, pulmonary tuberculosis, empyema, carcinoma of the lung, bronchitis, influenza, bronchiectasis, etc.

Alexander also classifies the cases of osteo-arthropathy as acute and chronic. In the acute cases the joint symptoms are prominent features. Alamartine concludes that the cases showing "Marie's syndrome" can be divided into three distinct and unrelated groups—a rare congenital condition; simple clubbing of the fingers (Hippocratic fingers); and subacute infectious osteo-arthritis. In the congenital cases, or cases which develop very early in life, there is hypertrophy of the terminal segments of the limbs, in which sometimes all the tissues and sometimes the bones alone are concerned. There is no pain or joint complications.

Since hypertrophic osteo-arthropathy is a secondary condition and not a well-defined disease, a large number of modifications may be expected. Of the 103 cases which Alexander collected, 26 were not typical. Bamberger's case seems thus far to be unique. In this all the long bones were more or less covered with a stratified layer of bone, porous in some places, harder in others, and most marked over the normal ridges and spurs to which muscles are attached. Here and there small areas of unaltered bone were left. No other cases have shown such extensive involvement (Alexander). Métin and Guillon[1] reported a case which, because of the shape of the hand,

[1] *Bull. méd.*, 1907, xxi.

and especially of the thumbs, they described as "hypertrophic pulmonary osteo-arthropathy of the acromegalic type." This patient was a consumptive. There were no changes in the face or head.

Diagnosis.—In every case of chronic pulmonary disease the appearance of pain and swelling near the joints should lead one to examine for hypertrophic osteo-arthropathy. The *x*-ray examination is very important. In a well-marked case the shadow of the sheath of new bone is clearly differentiated from that of the compact bone. The outline of the bones is usually smooth. The metacarpals are among the first to be affected. The terminal phalanges in cases of even very clubbed fingers are practically normal. The spicules of bone radiating from the tip of this phalanx are seen also on normal fingers.

With clubbed fingers one must not confuse Heberden's nodes. These are small exostoses at the proximal ends of the terminal phalanges on the dorsal side. They may be of even pea-size, and are sometimes painful. They are often associated with arthritis deformans. These phalangeal joints are often ankylosed, sometimes at an angle. Heberden's nodes are due to a thickening of the tubercles to which the tendons of the extensor muscles are attached. They are not the same as Bouchard's nodes, which are at the joints between the proximal and middle phalanges, and also at a point between the metacarpal and proximal phalanx of the thumb. They occur especially in patients with gastrectasis. Meynet's nodes are movable nodules in the joint capsule, sinews or sinew sheaths which occur especially in chronic arthritis. Multiple enchondromas are usually symmetrical. They occur on the hands and feet and on the terminal phalanges.

Bamberger's type is to be distinguished from chronic arthritis deformans. This is easy to exclude unless they co-exist. Marie's type should be distinguished from acromegaly. These diseases formerly were grouped together, although Doebbelin did call hypertrophic osteo-arthritis "pseudo-acromegaly." Any confusion is strange, since in acromegaly the hand is bigger and wider, the fingers are uniformly thickened and sausage-shaped, and the nails are small. In hypertrophic pulmonary osteo-arthropathy the fingers are clubbed and the nails are deformed. The shape of the long bones is very different and changes in the face occur only in acromegaly. In acromegaly one finds optical changes, glycosuria, early menopause, etc.

Prognosis.—The prognosis in this condition seems to rest entirely with the primary condition. The osteo-arthropathy seems to influence neither the general condition nor the course of the primary disease. The course of the osteo-arthropathy seems fairly acute for a time and the condition then remains stationary, but what in the primary disease determines either the appearance of the osteo-arthropathy, the time of its appearance, its duration, its severity or its distribution cannot be even guessed at. Granted that the immediate cause is a toxin from a focus of infection, the relative infrequency of the secondary condition and the absence of any observable relation to the course of the primary disease make one rather skeptical as to an immediate relationship between the two.

Treatment.—It is of course of prime importance to treat the primary disease, and marked improvement in the bony condition has followed successful treatment. One can do much to relieve the pains in the bones and joints. For this warm applications seem efficacious. Demons and Binant have used subcutaneous injection of lung extract with doubtful success.

PAGET'S DISEASE. OSTEITIS DEFORMANS. OSTITIS DEFORMANS.

There is a large group of diseases of the bones of which an even moderately reasonable classification has been, and is now, very difficult. We refer to the cases with general involvement of much of the skeleton, cases with diffuse involvement of one bone, and cases with lesions which began and for years were limited to one bone, but which later involved more, or most, of the skeleton. Pathologically there is a certain similarity in all these cases; one finds bone absorption and new bone formation; callus building and condensing osteitis; spontaneous fractures and various deformities, either angular, resulting from one local area of softening or fracture, or general, from a bending of the bone as a whole. Among the earlier terms used for these cases are osteomalacia, osteoporosis, osteosclerosis, etc. But these terms are merely descriptive of certain processes, all of which may exist in the bones of the same individual or, indeed, in the same bone, and are not names of diseases.

One of the earliest terms used of the diseases themselves is "rickets," and this term was used roughly of practically all bone diseases which caused extensive bone changes. Since then groups of cases have been separated from this general heterogeneous collection; infantile rickets, osteomalacia of pregnancy, luetic osteitis, tuberculous osteitis, achondroplasia, hypertrophic pulmonary arthropathy, general hyperostosis, osteogenesis imperfecta, etc.

The term *ostitis deformans* has long been used of various bone diseases which caused deformity of one or several bones. This term included nearly all the constitutional diseases of bone as we now know them, but also callus building in the repair of genuine fracture, of spontaneous fractures in lues, congenital deformities, etc. The cases now described as Paget's disease were formerly certainly grouped under this title (Sternberg[1]).

The term *osteitis deformans* was first used by Czerny in 1873 to describe a case of spontaneous curvature of the lower limbs. This was probably a case of "osteomalacia." In 1877 Paget used this term for that group of cases which he described as a separate disease, which disease now commonly bears his name.

Definition and Clinical Picture.—"From these five cases, which, although few, are well-marked and in some points uniform, as well as from a recollection of two more, of which I have no notes, I think we may believe that we have to do with a disease of bones which the following are the most frequent characters: It begins in middle age or later, and is very slow in progress, may continue for many years without influence on the general health, and may give no other trouble than those which are due to the changes of shape, size, and direction of the diseased bones. Even when the skull is hugely thickened, and all its bones exceedingly altered in structure, the mind remains unaffected.

"The disease affects most frequently the long bones of the lower extremities and the skull, and is usually symmetrical. The bones enlarge and soften, and those bearing weight yield and become unnaturally curved and mis-

[1] *Nothnagel's System*, 1903, Band vii.

shapen. The spine, whether by yielding to the weight of the overgrown skull or by change in its own structures, may sink and seem to shorten with greatly increased dorsal and lumbar curves; the pelvis may become wide; the neck of the femur may become nearly horizontal, but the limbs, however misshapen, remain strong and fit to support the trunk.

"In its earlier periods, and sometimes through all its course, the disease is attended with pains in the affected bones, pains widely various in severity, and variously described as rheumatic, gouty, or neuralgic, not especially nocturnal or periodical. It is not attended with fever. No characteristic conditions of urine or fæces have been found in it. It is not associated with syphilis or any other known constituent disease, unless it be cancer.

"The bones examined after death show the consequences of an inflammation, affecting in the skull the whole thickness, in the long bones chiefly the compact structure of their walls, and not only the walls of their shafts, but, in a very characteristic manner, those of their articular surfaces.

"The changes of structure produced in the earliest periods of the disease have not yet been observed, but it may certainly be believed that they are inflammatory, for the softening is associated with enlargement and with excessive production of imperfectly developed structures, and with increased blood supply. Whether inflammation in any degree continues to the last, or whether after many years of progress any reparative changes ensue, after the manner of a so-called consecutive hardening, is uncertain.

"Holding, then, the disease to be an inflammation of bones, I would suggest that, for brief reference, and for the present, it may be called after its most striking character osteitis deformans. A better name may be given when more is known of it" (Paget[1]).

Five years later Paget[2] reported additional cases and drew the clinical picture more graphically as follows: "It usually affects many bones, most frequently the long bones of the lower extremities, the clavicles, and the vault of the skull. The affected bones become large and heavy, but with such weakening of their structure that those which have to carry weight or to bear much muscular traction become unnaturally curved and misshapen. The disease is very slowly progressive and is felt only in pain, like that of rheumatism or neuralgia, in the affected limbs and in increased heat at the tibiæ. But neither the pain nor the heat are constant, nor do they continue during the whole progress of the disease; and pain has not been observed in the head even in the cases in which the skull was very thickened. There is not any clear evidence of general disturbance of health. In all the cases traced to the end of life, death has ensued through some coincident, not evidently associating, disease, which has been aggravated by the condition of the bones only in so far as they may have diminished the range of breathing and the general muscular activity.

"At present, with the exception of the seventh case, this disease has been observed as beginning only in persons over forty years old, and has appeared in no usual relation, whether by inheritance or coincidence, with any other

[1] "On a Form of Chronic Inflammation of Bones (Osteitis Deformans)," *Transactions of the Pathological Society*, London, 1877.

[2] "Additional Cases of Osteitis Deformans," *Med. Chir. Trans.*, London, 1882, lxv, 225.

disease except gout." (Case VII was a woman, aged fifty-eight years, whose disease began when she was twenty-eight years of age.) In conclusion he says: "In all of the cases I have seen the general appearance, postures, and the movements of the patients have been so alike that these alone might often suffice for the diagnosis of the disease. The most characteristic are the loss of height, indicated by the low position of the hands when the arms are hanging down; the low stooping, with very round shoulders and the head far forward, and with the chin raised as if to clear the upper edge of the sternum; the chest sunken toward the pelvis, the abdomen pendulous; the curved lower limbs, held apart and usually with one advanced in front of the other, and both with knees slightly bent; the ankles overhung by the legs, and the toes turned out. The enlarged cranium, square looking or bossed, may add distinctiveness to these characters, and they are completed in the slow and awkward gait of the patients and in the shallow costal breathing, compensated by wide movements of the diaphragm and abdominal wall, and in deep breathing by the uplifted shoulders. I have seen no case in which these characters are imitated except in those of ankylosis of the vertebræ and ribs, and which have been described by Dr. Allen Sturge under the name of spondylitis deformans; but these are easily distinguished by the lower limbs being naturally straight and the clavicles and skull unchanged."

Terminology.—A list of the various names which have been applied to this disease will be instructive as well as interesting: Ostitis deformans; Osteitis deformans (Paget); Paget's disease; Pseudorachitis senilis; Osteomalacia chronica deformans hypertrophica; Ostéite ossifiante diffuse (Lancereaux); Osteolysis (Lobstein); Hypertrophie spongieuse des os; Crâniosclérose; Hyperostose généralisée; Ostéite condensante; Ostéomalacie hypertrophique benigne; Pseudorachitisme senile; Rhumatisme ostéohypertrophique des diaphyses et des os plats; Osteomyelite fibreuse; and Sclerose osseuse hypertrophique.

Occurrence.—Paget's disease is a rather rare condition. Clopton was able in 1906 to collect but 75 cases from the literature. There have been but two cases at the Johns Hopkins Hospital out of over 20,000 medical patients. Sternberg stated that the cases were about equally divided between the sexes, but Clopton three years later reported that two-thirds of the cases were males. The two Johns Hopkins Hospital patients were males.

Etiology.—There have been very few etiological factors suggested for this disease. Lues, cancer, arteriosclerosis, nervous lesions, and gout have been mentioned.

As to the two Johns Hopkins Hospital patients, both had been hard workers, the one a potter the other a carpenter. The carpenter had had a sunstroke twenty-five years before admission, was ill for some months, and thinks his whole system suffered considerably. For many years he had had dyspepsia and diarrhœa and was very susceptible to any indiscretion in diet. The potter had always been a strong, fairly well man. He had rheumatism when sixteen years of age (he was sixty-seven years old on admission), "malaria" at fifty-one (while living in a truly malaria country), since which time he has had "rheumatism" in various joints. He had no gastro-intestinal troubles. The Paget's disease seems to have followed immediately after the "malaria."

Heredity.—There is good evidence that Paget's disease can be inherited. Chauffard mentions a mother and daughter, and Berger a mother and son similarly affected (Lannelongue[1]). Smith[2] mentions a father, seventy-four years old, who had Paget's disease of thirty-five years' duration, and his son forty-two years of age, with Paget's disease of three years' standing. It is very interesting that in both these cases the disease began when they were thirty-nine years of age.

Pathological Anatomy.—This disease affects especially the bones in the long axis of the body; the skull, spine, and long bones of the legs. The extent of the bony changes depends on the duration of the disease, but for a long time one or only a few bones may be involved. Often the long bones are asymmetrically affected. In some degree this is the rule, but the bones of one side may be entirely free or there may be a crossed involvement, for example, the left humerus and the right femur. The order of frequency with which the bones are involved is: the skull, tibiæ, femora, pelvis, spine, clavicles, ribs, and radii. The bones of the face, hands, and feet are least often affected. The skull is often from one-half to three-quarters of an inch thick. This increased thickness is due especially to a new bone formation on the outer lamellæ. Early in the disease this new bone is fine, porous, vascular, and so soft that it can be cut with a knife, but it hardens progressively until in ten or more years it may be like ivory, or becomes loose and friable. There is also some increase in thickness of the inner tables of the skull, but this usually remains dense white bone. The furrows for the vessels, especially the middle cerebral artery, seem deepened. There is obliteration of many or nearly all of the sutures. The number of nutrient foramina is greatly increased. Some emissary veins disappear. The horizontal circumference of the skull is increased. In one of Paget's cases it measured 71 cm.; in Stilling's, 64 cm. In the case reported by Hudela and Heitz[3] the skull is described as unchanged (the patient was a woman, aged seventy-five years). Of the bones of the face, as a rule, only the superciliary ridges are hypertrophied, and yet in one group of cases the bones of the face are much affected. This group of cases has been classified under the name hyperostosis cranii, supposed by Paget to be a distinct disease.

"The shafts of all the long bones are white, nodular and massive, and present an appearance of rugged strength and hardness which causes them at a distance to look as though hewn out of stone. The nodules are in the main smooth and rounded, but in parts, as, for instance, the upper end of the humerus, are craggy and irregular. The nutrient foramina are increased in size (and number)" (Waterhouse[4]). The deposits of new bone are placed especially along the normal ridges and projections. To a certain extent the result is an exaggeration of the normal.

The long bones of the legs are especially affected. The femur is much thickened and bent, with the convexity outward. The girth of this bone at its middle in Waterhouse's patient was five and three-quarters inches, and the bone was so curved outward and twisted on its long axis that its upper and lower articular surfaces faced in almost parallel directions. The beautiful arrangement of the cancelli at its ends is destroyed. The tibiæ

[1] *Bull. de l'acad. de méd.*, 1903, xlix, 299. Discussion.
[2] *Med. Soc. Trans.*, London, 1905, xxvii, 324.
[3] *Nouv. Iconog. de la Salpêt.*, 1901, xiv, 415.
[4] *Lancet*, 1907, i, 1215.

are most often, and often most markedly, affected. These bones are huge and very much bent, especially with the convexity forward, but also, and in some cases to an extreme degree, with the convexity outward, so that the bone is much arched. The fibulæ are also much thickened and bent. The tibia and fibula may be connected for some distance by a dense bridge of bone, which would certainly seem to suggest a peri-osseous inflammatory condition. The thickening of the tibia is especially on its anterior margins.

The bones of the upper extremities are much less affected, and yet the changes in these may be very marked. In a few cases the changes were only here for a time. The humerus may weigh more than twice as much as a healthy bone of the same length and the girth of this bone at its middle may be four and one-quarter inches instead of two and one-half inches as normal (Waterhouse).

The spine shows a marked kyphosis, even a definite knuckle. There is often partial ankylosis. The pelvis often shows no changes, although the bones are sometimes thickened. The appearance during life would indicate that the pelvis was much broadened. A heart-shaped pelvis similar to that in osteomalacia has been described.

The nature of these bone changes has been the subject of much careful study, and yet we have advanced little beyond the opinion of Paget. Stilling said that the disease begins as a chronic inflammatory process, a rarefying osteitis beneath the periosteum, and gradually involves the centre of the bone, with the formation of Howship's lacunæ, Haversian spaces, and perforating canals. But there is also new bone formation, both subperiosteal and myelogenous. The latter process gradually gains on the former, and so the bones thicken. The new bone is at first soft and yielding, and hence bends on pressure. The calcification may proceed irregularly throughout the bone, even leaving the cysts full of cloudy contents, or producing true bone tumors (Clopton[1]). Von Recklinghausen thought that osteomalacia was the first step, resulting in a marked reduction in the cortex which allowed the bones to bend. This was followed by an inflammatory process in the malactic areas, characterized by the formation of fibrous tissue (Clopton). Steele pictured the process as, first, the absorption of bone with the enlargement of the Haversian canals, then the formation of new bone which runs diffusely through the old portions. This new bone remains uncalcified and is, in turn, absorbed. The medullary substance is converted into vascular connective tissue. Lunn thought that constitutional conditions caused atrophy of much of the skeleton. This led to deformity of those bones most used, and that to a compensatory hypertrophy.

The result is a very variable picture. "The enlarged bones are abnormally dense or rarefied. The surface is smooth or rough, nodular or protuberant; the cortex thickened or thinned, spongy or eburnated; the cancellated structure sclerosed or coarsely trabeculated; the marrow spaces obliterated or transformed into cavities of various size. The central canal of the long bones is narrowed or dilated, even to disappearance, and the deformity of these bones is further increased by various degrees of abnormal curvature. There is no uniformity in the distribution of these alterations, and a single bone may be evidence of the decalcification, absorption, the formation of osteoid tissue and its calcification, which are the processes con-

[1] *Interstate Medical Journal*, 1906, xiii, 223.

cerned in the production of the gross changes. Multiplicity of the bones affected is the constant characteristic" (Fitz[1]).

It was at first supposed that the bends in the bones could all be explained as the result of tension, and that the new bone formation was a protective compensatory process. But this can hardly be true. Von Recklinghausen especially emphasized the idea that the hypertrophy was out of all proportion to the compensation and that the new bone was deposited where mechanics did not need it. For instance, in the case of the tibia the new bone is on the convexity, not the concavity, of the twisted bone. And in the case of the skull there can be no idea of strengthening a weak bone in the distribution of the new. He emphasized the importance of trauma and thermal influences in determining the intensity of the inflammation which produced the new bone. These bones are easily fractured and it may be this which leads to the diagnosis.

General arteriosclerosis is a practically constant lesion. The walls of the arteries may be so calcified that they show well on the skiagrams. This sclerosis need not be at all uniform, as in Hudela and Heitz's case,[2] in which the arteries of the brain, skull, and neck were normal, but those of the thyroid, liver, spleen, kidney, and adrenals were very thick, even obliterated. In this case the arch of the aorta and its thoracic portion were very soft, but the abdominal aorta and the arteries of the limbs were very sclerotic. Such a distribution of the aortitis is almost pathognomonic of lues. We may mention here the suggestion of Béclère that the bony changes were due to extreme sclerosis of the nutrient arteries of the affected bones. Hypertrophy of the heart is an almost constant feature. Valvular lesions, especially of the mitral valve, are common, and seem the result of atheromatous changes rather than of endocarditis.

Joint changes are rare, but one case is reported with the lesions of arthritis deformans in both knees.

The central nervous system has been carefully studied in the hope of finding here the essential lesion of this disease, but all the many lesions can best be explained as due to arteriosclerosis.[3]

Cases of Paget's disease have often had various tumors also. Among these are endothelioma (?) of the pleura and radius (Paget); carcinoma of the liver (Goodhard); tumor of the dura mater (Wilks); sarcoma of the tibia (Wherry); enchondroma of the pelvis (Lunn); cancer of the stomach (Moizard and Bourges). A few cases of Paget's disease have later had osteosarcoma, especially of the giant-cell variety.

As to the nature of the disease there has been much uncertainty. Some have even thought it not an independent disease, but an extreme grade of arthritis deformans. But most are willing to agree with Paget that it is an inflammation the nature of which little is known. Béclère[4] called attention to the marked arteriosclerosis in these patients and suggested that the bony changes are due to an especial involvement of the nutrient arteries of these bones. This would explain satisfactorily the variable and unequal

[1] *Transactions of the Association of American Physicians*, 1902, xvii, 398.
[2] *Nouv. Iconog. de la Salpêt.*, 1901, xiv, 415.
[3] See also Gilles de la Tourette and Marinesco, *Bull. et mém. de la Soc. méd. des Hôp. de Paris*, 1894, ii, 422.
[4] *Bull. et mém. de la Soc. méd. des Hôp. de Paris*, 1901, 3 s., xviii, 929.

distribution of the bony lesions. Others say it is due to arteriosclerosis of the nutrient vessels of the nerves.

One of the most interesting of recent suggestions concerning this disease is that held by several well-known Frenchmen that Paget's disease is of luetic origin. This idea, while suggested long before, was first seriously advocated by Lannelongue[1] in an article entitled "Note on Hereditary Syphilis of Bones in the Newborn (Parrot's Disease), in Children and Youths, in Adults, and in the Aged (Paget's Disease)." According to him, Paget's disease is a manifestation of hereditary lues of the aged. He based this opinion on the similarity of the lesions. Fournier[2] agreed with Lannelongue, and mentioned the cases of two brothers, the one of whom had hereditary lues and the other Paget's disease. Fournier later speaks of Paget's disease as a paraluetic condition, to be classed with tabes dorsalis, general paresis, etc. Auffret[3] followed this idea and reported a case of Paget's disease in a patient who probably had also hereditary lues, and mentioned other cases. The attempt was made by Robin[4] to differentiate Paget's disease from luetic osteitis by a comparison of the chemical composition of the bones. In a tibia with luetic osteitis he found water, 53.2 per cent.; fats, 0.1 per cent.; nitrogenous bodies, 21.6 per cent.; and mineral ash, 25.9 per cent. In a tibia from a case of Paget's disease these figures were 44.8 per cent., 13.1 per cent., 16.1 per cent., and 25.8 per cent. respectively. This, while interesting, is not at all convincing. Robin should prove that the bones from two cases of Paget's disease or two cases of lues do not differ as much as these, if only the stages of disease be different.

Symptoms.—The disease begins late in life, as a rule, the average age of onset being about fifty years. The youngest case reported began at twenty-one years, and one case began at eighty-two years of age. It is possible, however, that the disease exists for years before any objective signs appear. The onset in the two Johns Hopkins Hospital patients was at fifty-one and fifty-eight years of age.

The disease begins insidiously, usually with rheumatoid pains in the legs. The patient seldom notes the developing deformity. He may notice that he has to buy larger and larger hats (in Wherry's case the circumference of the head increased in four years from twenty-two and three-quarters inches to twenty-six inches), and he often complains that his legs are getting less and less serviceable, are becoming weak and awkward, and that he tires easily. But his friends will note that he is growing shorter, and that his legs are getting more and more bowed, the back bent, the arms relatively longer, and the whole appearance more ape-like. In French's case[5] the trouble began at forty-three years of age with the menopause. The bone changes usually begin in one tibia, then extend to the other, and then affect the other bones in irregular sequence. The bowing of the legs is both anterior and lateral. The lateral bowing is an interesting feature, since it may change a condition of knock-knees to one of bow-legs, and the result resemble a case of poorly treated fractures (Waterhouse's case). In Daser's case[6] the legs were so bowed that they crossed below the knees. In some

[1] *Bull. de l'acad. de méd.*, 1903, 3 s., xlix, 299. [2] *Ibid.*, p. 532.
[3] *Rev. d'Orthopédie*, November, 1905.
[4] *Bull. de l'acad. de méd.*, 1903, xlix, 532.
[5] *Clin. Soc. Trans.*, 1904, xxxvii, 213. [6] *Münch. med. Woch.*, 1905, ii, 1635.

the trouble begins in the skull. When once begun the disease is usually progressive, although it may remain limited to one bone for years, and it attacks a very variable number and assortment of bones. For instance, in French's case the disease for the first six years was confined to the left tibia. The disease seems to progress until the patient's death, and yet this is the result of intercurrent infections, cancer, or accidental causes, for Paget's disease does not seem to shorten life.

The clinical picture given by Paget is so graphic that we will merely add that the opinion of many is that leontiasis ossea is a form of this disease. If this is true, then changes in the skeleton of the face may be marked, the disturbance in the cranial nerves and the headache may be severe, and there may be symptoms of mental disorders.

The stature may shorten even one foot, owing to the kyphosis of the spine and the bowing of the legs. In one of the Johns Hopkins Hospital patients the shortening seems to have been more than a foot. His height on admission was four feet six and one-quarter inches. Fractures of the involved bones are not infrequent, and may call attention to the condition (Clopton reports such a case). Pain in the legs, especially below the knees, usually of a "rheumatic" character, is the commonest symptom of onset. These pains may precede the visible changes in the skeleton by several years. In one case they began as "growing pains" when the patient was a young girl. The pains are sometimes "in the arms and legs and around the hips, more in the muscles and sinews than in the bones and joints." They may be worse at night, and often seem to depend on changes in the weather. In some cases these pains are entirely absent, while others and especially those with marked spinal curvature, have pain only on motion. So much do cases vary as regards pains that Joucheray separated a "painless" and a "painful" variety of Paget's disease.

The thorax becomes narrow, the ribs immovable, and finally the respirations may be purely diaphragmatic. There are almost no symptoms on the part of other organs, the patients feel "well," for Paget's disease seems to have little influence on the general health. Some patients do complain of bronchitis, which is not remarkable considering the rigidity of the chest wall, while cardiac disturbances, valvular and myocardial, are not rare, which is easily explained by the degree of arteriosclerosis.

Of the Johns Hopkins Hospital patients, one came complaining of dropsy, dimness of vision, and stomach trouble. One year before he began to have lassitude, weakness, shortness of breath, and quite general œdema. For several weeks he had stiffness of the neck, pain over the left eye, and at the occiput. He had much arteriosclerosis, considerable kyphosis, and a marked pigeon-breast. His head was one-half inch larger than before, and he was three inches shorter. The deformities of his bones were characteristic. There was little evidence of heart disease; in the urine there was a trace of albumin, but no casts. The changes due to Paget's disease had scarcely attracted his attention. The other patient with Paget's disease of fifteen years' duration, came complaining of "asthma." He had had considerable headache recently, loss of vision (double cataract), and deafness. He had very poor control over both bladder and rectum. There was marked kyphosis and sclerosis, mainly in the mid-dorsal region. The scoliosis had its convexity to the right, and caused great asymmetry of the chest. The deformity of the lower extremities was marked, but there was also some bowing of the bones of the arms. He had lost thirteen inches in height.

Melanoderma was an interesting feature of Hudela and Heitz's case.[1]

Emphasis has been laid on the claim that in Paget's disease the mind is unaffected, and yet in Fitz's case[2] the condition of "mild stupor, depression, and delusions" was sufficient to necessitate confinement in an asylum.

Diagnosis.—A fully developed, well-marked case of Paget's disease can usually be recognized at a glance, but an early diagnosis is often impossible. These patients may be treated for years for "muscular rheumatism," "chronic rheumatism," neuralgia, sciatica, senile marasmus, arteriosclerosis, etc. The cases with involvement of one bone are particularly difficult of diagnosis, for, after all, "multiplicity of the bones affected is the constant characteristic" of Paget's disease. But to apply this criterion would mean that the diagnosis could not be made until the disease had fully developed, that is, had involved many bones, and this might mean a delay of years, and a diagnosis could never be made in the case of those who "died too early." Since the disease may remain limited to one bone for years, and since it may begin at eighty years of age or over, the difficulty is apparent. This difficulty of diagnosis is important, since some of the cases from the study of which interesting deductions have been drawn may not have been Paget's disease (*e. g.*, the value of the interesting blood and urine findings in the man studied by Apert, Bornait, and Legueule,[3] depends entirely on the accuracy of that diagnosis; the same may be said of the cases cited in the discussion concerning its luetic origin). There is still a dispute whether the diagnosis can be made after death from the gross microscopic or chemical study of the involved bone. Many pathologists (*e. g.*, v. Recklinghausen) believe that the pathological bone changes are not specific, others (*e. g.*, Stilling) believe that the diagnosis could be made by the microscopic study of the lesions if the pathologist has several bones at his disposal. If, then, a careful pathological study does not always give a diagnosis, how difficult must be the clinical diagnosis! The diagnosis of lues is a natural mistake, especially when one tibia only is affected. When fully developed one must exclude osteomalacia, spondylitis deformans, acromegaly, hypertrophic pulmonary osteo-arthropathy, and neoplasm. The differential diagnosis between Paget's disease and diffuse or tuberculous hyperostosis will depend on one's ideas of the latter condition.

Osteomalacia.—In a certain degree this term may include Paget's disease, and it is quite possible that the group as it now stands and out of which the cases of Paget's disease were taken is susceptible of considerable further subdivision. There are two forms which have a fair claim to be called clinical entities; the osteomalacia of pregnancy especially and possibly senile osteomalacia. The points in common of osteomalacia and Paget's disease are kyphosis, shortening of stature, bending of the limbs, and rheumatoid pains. But in osteomalacia there is no hypertrophy of bones, the bones are symmetrically affected, the deformities begin in the skeleton of the trunk and involve the bones of the extremities less and later, and the skull only in the severest cases, and the pains are much less pronounced. The puerperal osteomalacia begins in the pelvis and lumbar spine and these patients have a paretic gait. In the cases of senile osteomalacia pain is a very prominent feature. These patients are bedridden early.

[1] *Nouv. Iconog. de la Salpêt.*, 1901, xiv, 415.
[2] *Transactions of the Association of American Physicians*, 1902, xvii, 398.
[3] *Bull. et mém. de la Soc. méd. des Hôp. de Paris*, March 14, 1907, p. 235.

Hyperostosis Cranii.—In hyperostosis cranii the lesions are described as chiefly of the skull, with hyperostoses, signs of intracranial pressure, and cerebral nerve paralysis. But Sternberg admitted that there are borderline cases between this and Paget's disease, and now it is believed that they are all one disease.

In *hypertrophic pulmonary osteo-arthropathy* the long bones are not at all bent, the ends only of certain bones are involved, the fingers are much affected, and the cranial bones are entirely free of changes.

Spondylitis deformans, with the involvement of the spine and large joints, may resemble early cases of Paget's disease, but the entire absence of changes in the long bones is a fundamental difference.

Acromegaly.—Acromegaly bears only a superficial resemblance to Paget's disease. In both there is enlargement of the head, kyphosis, and thickening of the long bones. But in acromegaly the bony lesions are symmetrical. There are characteristic changes in the soft tissues which entirely fail in Paget's disease, and the bones of the face are enlarged rather than those of the cranium.

Prognosis.—Paget's disease seems to have almost no influence on the general health. Of course, if the cases of general hyperostosis be included under this heading then the above statement must be modified to read that the prognosis will depend on the local pressure (*e. g.*, on the brain) exerted by the bony tumors. But even a classic case of Paget's disease possibly is more susceptible to acute troubles than is the normal man of his age. One might expect that the lungs, hampered in their function by the deformed thorax, would suffer from emphysema, chronic bronchitis, etc., as do they in the various forms of arthritis with ankylosis of the ribs. These patients usually have arteriosclerosis of a rather severe grade and suffer from the conditions secondary to this condition. And yet, all things considered, the cases of even marked grades of Paget's disease do enjoy fairly good health.

Treatment.—There is no treatment of any benefit. One can give the various antineuralgic remedies for the pains, and especially iodine and quinine. If the lesions are luetic one would expect them to improve under antiluetic treatment, which is not the case (yet this is no strong argument against the luetic origin of the disease, for late luetic lesions are little influenced by this treatment, and paraluetic lesions not at all).

Tumor-building Osteitis Deformans (v. Recklinghausen). General Hyperostosis of the Skeleton with Cyst-building (Virchow). Osteomalacia with Cyst-building (Hirschberg).—This condition seems to be intermediate between Paget's disease and multiple primary neoplasms of bone. The skeleton is much deformed by multiple hyperostoses, fractures, pathological curves, and definite tumors and cysts. In the medullary canals in one case (v. Recklinghausen) were multiple fibrocystomas, in another case at exposed points giant-cell sarcomas with cyst formation. In Virchow's case there were colossal hyperostoses of the skull and hyperostoses and curves of some long bones, but osteoporosis of others. In Hirschberg's case there were multiple sarcomas, with cysts and multiple fractures.

OSTEOGENESIS IMPERFECTA.

Osteogenesis imperfecta,[1] Vrolik,[2] Stilling.[3] Periosteal dyscrasia. Osteomalacia congenita (Jürgens). Rhachitis annularis. Chronic parenchymatous osteitis (Schmidt). Fragilitas ossium congenita (Klebs). Periosteal aplasia (Klebs). Osteoporosis congenita and osteosclerosis congenita (Paltauf). Osteopsatyrosis.

This group of diseases seen in fetuses, stillborn infants, and very seldom in the living child, formerly all diagnosed "fetal rickets," without doubt includes a variety of quite different conditions. The lesions in these skeletons vary so that a comprehensive description is almost impossible. The cases known both as "annular rickets" or "multiple intra-uterine fractures" are considered by many as the fetal form of osteopsathyrosis of adults. The cases of osteomalacia congenita are regarded by Jürgens as the congenital form of osteomalacia of adults. These newborn infants are often thin, very wrinkled and with poor muscular development, in marked contrast to those with achondroplasia. The condition is not evident from superficial observation, since the body proportions are fairly normal.

In achondroplasia the disease would seem to affect the epiphyseal cartilages. The diaphyses of the bones are strong and often of almost ivory hardness; that is, the subperiosteal bone formation seems normal. In osteogenesis imperfecta, on the other hand, the subperiosteal bone formation seems involved, and the epiphyses little or none. The bones are of normal length, but are soft or fragile. They present angular deformities, "false joints," "callus masses," and other lesions which are explained as "healed or partially healed fractures." Sometimes the bones are so soft and pliable that they can be bent in any direction without crepitation. In other cases the diaphysis consists of alternate segments of cartilage and bone. In still other cases the bones are slender and brittle, and in some they contain only parchment-like lamellæ of osseous tissue. Each rib may be studded with cartilage knots, and the long bones present a succession of thickenings along their diaphyses. The pelvis may resemble that of osteomalacia. The skulls of these infants are especially interesting. The vault of the cranium is a membranous pouch in which is one (in Stilling's case in the forehead) or many little islands of bone, with jagged stellate margins. In other cases, with fairly extensive ossification, the skull is parchment-like. The base of the skull and the bones of the face are normal.

Etiology.—These fetuses are almost all born dead. It is possible, however, that osteopsathyrosis in children may represent a survival of certain mild cases. Many of these cases are one of twins, the other child normal. The first idea was that all were examples of "fetal rickets." Many still hold the theory of multiple intra-uterine fractures.

Intra-uterine Fractures.—Under this heading may be grouped a variety of cases. In some infants one or more bones are actually broken, usually during or recently before delivery. Genuine fractures are usually single. Bouchaut[4] reported a case in which fracture of the thigh of the fetus was due to a fall of the mother six weeks before the birth of the child. While genuine

[1] Schuchardt, *Deut. Chir.*, 1899, vol. xxviii.
[2] *Thesis*, Leipsic, 1854.
[3] *Virchow's Arch.*, 1889, cxv, 366.
[4] *Maladies des Nouveau-nés*, Paris, 1862.

fractures of a normal fetus knit rapidly, in these cases with supposed fractures there must be slow healing, with the formation of a false joint, due to the atrophy and pointing of the ends of the bones, or even spaces without any bones at all; 70 per cent. of such fractures are of the femur. The humerus and clavicle follow in order of involvement.

In other cases the bones are obviously very fragile. They consist of parchment-like lamellæ of bone, which fracture on the least pressure. By far the most, however, show enlargements along the shaft, suggesting callus formation following a fracture, others show angular deformities, which one attempts to explain as the result of fracture. There is ground for strong doubt, however, that many, if indeed any, of these cases are really fractures. It is difficult to believe that direct violence can produce the multiple "fractures" (even 113 in Chaussier's case) which these infants show; these bones are not always more brittle than normal; the callus and angular deformities are at positions (*e. g.*, near epiphyses) where a mechanical pull or a blow would not be likely to fracture the bone; and finally there is a suspicious symmetry in the arrangement of these bony rings. The cases with evidence of multiple fractures, or multiple callus formations, have long borne the name "annular rickets." The rings of callus on these bones are explained by those holding the rickets theory as irregular proliferations of the periosteum. The angular deformities which some explain as due to the healing of a fracture in a malposition are often, and some think usually,[1] due to ingrowths of periosteum between diaphysis and epiphysis on one side of the bone only, and so inhibiting the growth of the bone on this side. In favor of the view that these lesions are developmental abnormalities rather than fractures is the partial or total absence of the fibula when the tibia is involved.

Some cases of this group seem due to lues. Sutherland[2] reported the case of a living child whose condition was due possibly (although not certainly) to syphilis. This child presented "fractures" of all of the long bones and of many of the ribs. It recovered under mercurial treatment. Bouchut's[3] case, No. 3, was possibly luetic. The case reported by Daniel[4] with deficient bone formation in the vault of the skull and fracture of the humerus may belong in this group.

Pathology.—Histologically,[5] the cartilaginous ossification is normal, but the subperiosteal is abnormal. The osteoblasts are few and scattered; the osteoclasts are abundant. The result is faulty bone formation and the reduction to thin lamellæ of the diaphyseal cortex which had been formed.

OSTEOPSATHYROSIS.

Osteopsathyrosis (Lobstein, 1833). Fragilitas ossium (Klebs). Lobstein's disease. This rare condition characterized by abnormal brittleness of the bones occurs in infancy, childhood, and adult life. Many think that osteogenesis imperfecta of fetal life is the same disease. It is probably nearer the truth that among the cases grouped under osteogenesis imperfecta are cases of osteopsathyrosis.

Abnormal fragility of the bones occurs in old age (senile osteoporosis) and in cases with inaction atrophy, in cases of cachexia (especially that due

[1] Kaufman, *Beitr. f. Path. Anat.*, 1893.
[2] *Clin. Soc. Trans.*, 1907, xl, 263.
[3] *Maladies des Nouveau-nés*, Paris, 1862.
[4] *Ann. d. Gyn. et d'Obstet.*, 1903.
[5] *Durante Rev. méd. de la Suisse romande*, 1902, p. 809.

to malignant disease), in various diseases of metabolism, as rickets and scurvy, in certain nervous diseases, as locomotor ataxia, general paresis, and anterior poliomyelitis, and in general intoxications, as phosphorus poisoning. Among the insane a special form of fragilitas ossium occurs, which is due to rarefaction of the bones. The atrophy of the bony tissue in these cases may be marked. This is ascribed to the poor nutrition of these patients and the frequent traumas which they suffer. Local brittleness of bones may be due to the local osseous lesions of lues, osteosarcoma, the metastases of carcinoma in bones, multiple myelomas, and echinococcus cysts of bones.

But in all the above conditions examination of the fractured bones will reveal local lesions, or gross or microscopic changes in their structure, which easily explain their brittleness. The term osteopsathyrosis, or Lobstein's disease, etc., is reserved for "idiopathic cases," "without (as yet) demonstrable lesion." And yet radiographs of the long bones of these cases would suggest a rather thin cortex, slender shafts, and for this reason, perhaps, epiphyses, which are apparently enlarged. These cases seem rare, since so few are on record (only about twenty were reported during the last decade), and yet they are not so very uncommon.

Etiology.—The sexes are equally affected. In a rather large proportion of the cases the condition is inherited from generation to generation, and in still more cases it affects several of the same generation.

If osteopsathyrosis is osteogenesis imperfecta of viable infants, then the lesion is an inability of the periosteum to develop a sufficiently thick cortex. Some think that there is relatively overactive absorption of the cortex. Some think it secondary to changes in the nervous system. Lipschütz thinks the lesion lies in the cancellous tissue, since in his case the fractures involved not the shaft, but the extremities of the bones, and the skiagraphs showed that the trabeculæ were abnormally few.

The general health of these patients would appear to be excellent. The fractures follow very trivial injuries, as a slight blow, muscle pull, a fall, and turning over in bed. Simple chewing may fracture the jaw. The long bones are the ones most frequently broken. The number of fractures which these patients may have during their whole life varies from a few to more than one hundred.

This disease affects especially the period of development. The fragility would seem to vary much at different periods of life, for the first fracture may occur during birth, during the first bath, or much later, even in the fourteenth year. In most cases the condition ceases at thirty years of age, but in one case it continued until the seventieth year. In some cases the bones would seem to be at first soft and pliable, and later rigid and fragile.

Symptoms.—Usually the fractures are rather painless. As a rule, they knit quickly, more rarely slowly. The amount of callus thrown out varies much. The patients usually are markedly deformed. These deformities are due for the most part to the union of the fragments in bad positions, and yet some of the deformities develop during a stage when the bones are abnormally soft and pliable. This applies especially to the pelvis. The tibia is often sabre-shaped, wide, and flattened laterally. In one case there was progressive ankylosis of the joints.

Prognosis.—Osteopsathyrosis can make a patient wretched for years, and yet in middle life the bones seem to become stronger, since the fractures are

less frequent. In these cases the prognosis is one of function rather than life, for this disease does not seem to influence the duration of the latter, while the deformities resulting from union in faulty positions may be a great calamity to the patient.

Treatment.—The only medication suggested which seems to have been beneficial is phosphorus (Pouvier[1]). Of course, the treatment of the fracture is a surgical problem. Great care should be taken to prevent deformities, since when the condition has ceased this will spare the patient great inconvenience afterward.

GENERAL HYPEROSTOSIS; HYPEROSTOSIS OF THE SKULL, LEONTIASIS OSSEA (VIRCHOW).

In these conditions the distribution of hyperostosis is in nearly all cases fairly general. In those cases termed "general hyperostosis" the skull is usually more affected than is the rest of the skeleton, and in the cases termed "hyperostosis of the skull" the condition is general, but over the rest of the skeleton of a grade so mild that it is easily overlooked.

This condition has been an interesting subject of study since Malpighi reported the first case on record. But for a long time the general picture of the condition was erroneously drawn because it was made from the study of skulls preserved in museums and without examination of the other bones of the skeleton It is only recently that clinical reports of these cases have been published. Many undoubtedly have been diagnosed as acromegaly.

The tendency to-day, and especially among American writers, is to consider that this condition and Paget's disease are modifications of the same condition.

General Hyperostosis of the Skull, Leontiasis Ossea (Virchow), Cephalomegalia, Megalocephalia.—These names have been given to a rare condition characterized especially by diffuse hypertrophy of the bones of the skull. All the bones of the face and cranium are affected, but in varying degree. The hypertrophy is diffuse, yet the surface of the bones is rough. There are no large exostoses. The air sinuses of the bones of the face practically all disappear and the orbits are much encroached upon. The result is a huge skull weighing even 4000 grams, and much distorted. The sutures disappear, the foramina, especially those for nerves, are narrowed, these and the grooves for the vessels are some of them widened, some narrowed, causing stenosis of the vessels, and some are obliterated, necessitating considerable change in the circulation. In some cases the thickened bones are as hard as ivory, in others the cancellous tissue is retained.

The present interesting question is the relation of this condition to osteitis deformans. Paget considered the two diseases distinct. Sternberg[2] admitted that there were border-line cases which might be either. Since Sternberg's report the opinion has gained ground that hyperostosis cranii is not a disease entity, but a condition common to perhaps several diseases. The early descriptions of these skulls were in part based on the study of museum specimens. No other bones of the skeleton were available for

[1] *Thesis*, Paris, 1907.

[2] *Nothnagel's System*, 1903, Band vii.

examination, or the lesions of other bones were so slight that sufficient attention was not paid to them. But the similarity of the lesions of the skull itself were so like those of osteitis deformans, varying only in degree, that there has always been difficulty in differentiating them. Sternberg drew the clinical picture from a study of twelve reported cases, and yet of these one (Hale White's[1]) turned out later to be a case of syringomyelia with only an apparent hyperostosis cranii; at least one other (Ede's case[2]) turned out later to be Paget's disease, and the same may be true of other cases had they been followed longer. Another was later shown to be lues (Putnam). Prince[3] said in conclusion: "We have no sure ground for differentiating hyperostosis cranii from osteitis deformans. Both are probably trophic disturbances, perhaps allied, and possibly only different manifestations of one and the same disease." Of course, the differences cannot be overlooked. The cases described as hyperostosis cranii have, for the most part, developed at an earlier age than the majority of cases of Paget's disease. The lesions on the skull are much more marked, and the symptoms from them much more pronounced than in typical Paget's disease. But these differences are by no means sufficient to differentiate the conditions. They are symptoms which one would expect who considers the anatomical findings. We have only to assume a difference in the localization of the process common to Paget's disease and this condition.

Clinical Course and Symptoms.—Of the 21 cases collected by Prince, only 10 began after thirty years of age, and of these only 4 after forty years. The disease begins insidiously, the first symptoms often in late childhood or puberty. There is a general increase in the volume of the skull and a marked bulging of the forehead. The result is a huge, misshapen head. Soon, and often before the increase in the size of the skull is noted, begin headache, sometimes continuous, sometimes paroxysmal, and the symptoms from compression of the nerves in the foramina, neuralgia, blindness, deafness, bilateral facial paralysis, and disturbances in chewing, swallowing, and breathing, with paralyses. The circulation of the head changes considerably, owing to the stenosis or obliteration of the vessels in the foramina. Some subcutaneous veins may be very much distended. Stenosis of the canalis caroticus may cause a loud roaring in the ears, diminished by pressure on the carotid artery (Putnam). Exophthalmos is often present. Insomnia and mental apathy develop later; mental disturbances are common; epileptiform convulsions and finally paralysis of the extremities "complete the sad picture." Death follows from inanition or paralysis of the muscles involved in mastication and swallowing, or, as often happens in cases of chronic intracerebral compression, it may come suddenly with convulsions. The duration of the disease is given as from twenty to thirty years.

Nodular Hyperostosis of the Skull.—This form of leontiasis ossea differs from the preceding or diffuse form in that the hyperostoses are definite tumors on a fairly normal bone. These tumors may be flat or mound-like, and are of various sizes and shapes, but are seldom prominent and warty. The underlying bone is not perfectly normal, but is the seat of a diffuse hypertrophy of varying degree. The results are hideous deformities. The most common situation for these tumors is the cranium.

[1] *Brit. Med. Jour.*, 1896, p. 1377. [2] *Amer. Jour. of the Med. Sci.*, 1896.
[3] *Transactions of the Association of American Physicians*, 1902, xvii, 382.

Situated here they may grow inward, exerting pressure on the brain. In some cases the tumors at first are limited to the lower jaw, but later develop on other bones as well. One form, in which the tumors are for a long time at least limited to the jaw bones and are symmetrically placed, has been described as an independent disease under the name "hyperostosis maxillarum."

So often is this condition combined with giant growth that Sternberg suspects some relation between these two conditions. A somewhat similar although much less marked development of hyperostosis is seen in idiots and the insane.

Pathology.—Pathologically these hyperostoses cannot be sharply differentiated from exostoses and osteomas. They cannot always be differentiated from sarcomas, even on microscopic examination. Gummas must be excluded.

Symptoms.—The tumors develop slowly and cause symptoms which depend on the organ pressed against. The most important group of symptoms are those resulting from pressure on the brain, on the eyeball, on the respiratory passages, etc.

Prognosis.—The prognosis depends on the situation of the tumors. When their pressure does not interfere with the function of any important organ the disease may not appreciably influence life. The deformities may be hideous, and while the effects of pressure from such slowly growing tumors may be much less marked than from the more rapidly growing ones, yet these patients may suffer severely.

Treatment.—The treatment must be local, since the cause of the condition is not yet known. It is always well to try antiluetic treatment in the hope that this may benefit the patient, but this failing the surgical removal of those tumors whose presence is a menace to life or a detriment to important functions is indicated.

Daireoff[1] thinks that in addition to the above forms there is another group of the systematic osteopathies which he describes as *deforming hyperostosis.* This affects symmetrically the inferior epiphyses of the bones of the legs and forearms and the bones of the feet and hands. The result is elephantiasis-like extremities. The osseous hypertrophy develops slowly, and is preceded by a period of functional trouble. It seems a trophic disturbance.

MICROCEPHALUS.

The most important features of microcephalus, or abnormal smallness of the head, and hence of the brain, are retardation in the development of the cerebral cortex and mental reduction. Slight degrees of microcephalia are much commoner than macrocephalia or hydrocephalus, but marked grades of microcephalia are very rare.

The cases of microcephalus may be divided into two groups—those the result of antenatal disease and those due to developmental deficiency. The latter, the "idiopathic" cases, not due, so far as we can see, to antenatal disease, are ascribed to "inhibition" of growth of the brain due to pathological "feebleness" of the embryonic tissue from which the cerebral hemisphere

[1] *Thesis*, Paris, 1900.

will develop. This is the "atavistic" group, or the "primary" group of Giacomini. While these cases may be relatively numerous, as yet but one case has been carefully studied pathologically and every trace of antenatal disease excluded (Hilty[1]). This case was that of a woman, aged forty-nine years, whose brain weighed but 370 grams. The convolutions were abnormal in their arrangement. The woman had also a parenchymatous goitre. He states that this woman's mentality was much better than one would expect.

If we accept the cases reported as primary as correctly diagnosed, the following is the picture: The size of the cranium may be that of a newborn child, the smallest head on record being twelve inches in circumference. This patient was a child, twelve years old (Shuttleworth). The cranium, although small, is often well-shaped. The face is always relatively and sometimes absolutely large. The brain is small, with primitive arrangements of the convolutions. The sutures of the skull are normal. The brain does not grow, and hence the skull also does not. There are no indications of intracranial pressure, and no signs of brain lesions, such as motor disturbances, convulsions, etc. The reflexes are usually normal. Coördination of all the voluntary movements is perfect and the movements sometimes remarkably quick, being described as ape-like (Jones[2]). The intellectual development varies much. Walking is delayed (*e. g.*, to the fourth year). Some of these patients never try to talk, and yet they may be able to recognize their friends.

In the second group the microcephalia is due to antenatal intracranial disease. What these diseases are has led to considerable dispute. They seem to belong, in part, to those producing hydrocephalus, in part, to those producing porencephalus. The head is small and very narrow laterally, hence reresembling a tent; the forehead is very narrow, pointed above, and receding. The sutures seem prematurely united. In these cases motor disturbances, spastic paraplegia, and anæsthesias occur, and the reflexes are usually exaggerated.

Among these cases there may be a few in which the premature union of the sutures is primary and the brain cannot grow, since the cranium cannot expand. It is for these cases that operation has been performed, with very doubtful results.

FACIAL HEMIATROPHY.

Synonyms.—Neurotic progressive facial atrophy. Hemiatrophia faciei progressiva (Parry, 1825).

In this disease there is a slow, progressive wasting, first of the skin (some say of the fat), then of the subcutaneous tissue, later of the bones, and last and least of the facial muscles. Only one side of the face is affected, seldom both. Not over 200 cases are on record (Eulenburg[3]). Women are much more affected than men. The left side is more often affected than is the right. It is a disease which begins in the majority of cases during childhood and youth, and there is good evidence that the condition often has a congenital anlage. As immediate causes have been mentioned exposure

[1] *Arb. aus d. Hirnanat. Inst. in Zürich*, 1906, ii, 205.
[2] *British Journal of Children's Diseases*, 1905, ii, 214.
[3] *Eulenburg's Real. Encyclopädie*, 1908, v, 750.

to cold, insignificant traumas, and acute infectious diseases. Believed formerly by some to be due to disease of the local tissues, it is now granted by most to be due to disease of the trigeminus of the affected side. In the only well-reported autopsy the terminal stage of an interstitial neuritis from origin to periphery of all branches of the fifth nerve, especially the superior maxillary branch, was found. The cervical sympathetic nerves also are sometimes affected, and in one case a similar lesion of the left radial nerve was found, with atrophy of the muscles and skin which it supplies.

The course is slow and progressive until the atrophy reaches a certain grade, and then the condition may for a long time remain unchanged. The onset of the atrophy, usually insidious and without any symptoms, is sometimes for a long time preceded by sensory and motor symptoms in the region of the fifth nerve of the side later affected; neuralgic pains, hyperæsthesias, paræsthesias, spasm of the masseter muscle, and epileptiform convulsions are reported. Spontaneous improvement may occur during the course of the disease.

Symptoms.—The first symptoms may be one or several later coalescing patches of leukoderma with thinning of the skin at these points. But in most cases the lesion begins diffusely. The area of these patches increases; the subcutaneous fat gradually disappears, and soon the skin seems attached directly to the bone. The bones, especially the superior maxillary, are early affected, and the muscles last and least. The hair of the scalp, the eyebrows, eyelashes, and the beard over the affected area may fall out, or turn white—diffusely or in patches. The activity of sebaceous glands ceases, that of the sweat glands may continue almost normally. The skin becomes rough and hard, and resembles somewhat scleroderma. The patient complains of twitching of the skin, of a drawn feeling. The sensations of the skin are little affected, the skin reflexes remain normal, although the vasodilator reflex on that side may be lost. The eyeball sinks because of the loss of orbital fat. The muscles of mastication become weak early, but the facial muscles are little involved. The half of the tongue and soft palate corresponding to the facial involvement are not always but sometimes markedly atrophied. The bones of the face waste, and so their normal eminences become less prominent. The alveolar process especially suffers and the teeth drop out. The features are gradually drawn to the affected side. The result is that the affected side of the face becomes much smaller than the other, and the two sides seem like the faces of different persons. The lesion stops abruptly at the mid-line.

Diagnosis.—In the diagnosis one must exclude scleroderma, the atrophy following nuclear lesions and paralysis of the cervical sympathetic nerve, that following anterior poliomyelitis, and the facial atrophy seen in hemiplegia of infants and adults. The face is asymmetrical in congenital wrynecks. The normal side looks atrophied in a case of acquired facial hemihypertrophy.

Prognosis.—This condition does not seem to influence appreciably the general health. When once it begins there is nothing which seems to stay its course, and the periods of improvement which do occur cannot be attributed, so far as we can now say, to any therapeutic measure.

Treatment.—There is no treatment which affects the course of the disease. The appearance of several patients has, however, been much improved by paraffin injections.

PART VI.

MEDICAL ASPECTS OF LIFE INSURANCE.

By CHARLES LYMAN GREENE, M.D.

Life insurance is intrinsically a philanthropic enterprise rather than a business undertaking, inasmuch as it seeks to partially indemnify the dependents of an insurer for the pecuniary loss incident to his death, and, in spite of the complicated machinery which has been brought into play by modern life insurance companies, the underlying principles are of the simplest description. This very simplicity has led to life insurance based upon unsound methods, and has also been unnecessarily obscured by the issuance of a vast number of complicated policy forms. In most instances these forms are intended to catch the fancy or meet the convenience of the insurer, or to combine with pure insurance the endowment feature.

Assessment insurance represents the simplest form, but, in spite of many modifications, has proved in most instances to possess a dangerous lack of certainty and permanence.

The so-called *level premium insurance*, also known as "old line," is absolutely safe and permanent, provided the management be honest and the inspection by State or National authority searching and efficient. It provides for an arbitrary annual payment per thousand of insurance, the payment being so adjusted as to be greatly in excess of the expected loss during the earlier years. From this excess a fund is created (reserve) which will take care of the increasing cost of the later years of insurance. Reserve is actually *unexpended net premium*, and a company so organized should be able to cease taking new business at any time and yet pay every obligation as it falls due. The following simple example may suffice to explain the principles involved:[1] Assuming: (1) That a certain number of individuals desire to make provision for their families in event of their death. (2) That each is willing to pay annually such a sum as will at once create and afterward maintain a fund sufficient for this purpose. (3) That for purposes of convenience a company is organized to receive the individual subscriptions and to make the required payments to the families of deceased members. It follows then—

(*a*) *That the company becomes "the insurer."*

(*b*) *That the subscribers are "the insured."*

(*c*) *That the family represents "the beneficiary."*

(*d*) *That the individual subscription represents "the premium."*

(*e*) *That the contract which guarantees the payment of a fixed sum to the beneficiary represents "the policy."*

(*f*) *That the sum to be paid the beneficiaries represents "the amount insured."*

[1] *The Medical Examination for Life Insurance* (Greene.)

In order to fix the premium it is necessary to determine: (1) The amount to be paid to the beneficiary. (2) The additional amount necessary to provide for the expense of maintenance and operation of the company. This constitutes the "loading for expense." (3) The amount necessary to be carried on hand from year to year to meet death losses as they occur, or to be put aside and invested to meet the inevitably greater loss of the later years of insurance. This constitutes "the reserve."

The following example is based upon one contained in Willard's *The A, B, C, of Life Insurance: It is assumed that* 1000 *men wish to insure, that each is forty years of age, is insured for* $1100, *and remains insured until death.* Mortality tables show the number likely to die in each year, but to simplify matters it may be assumed that ten years is the maximum life and 100 deaths per year the expected loss, both purely fictitious suppositions. The company's total obligation is represented by the amount guaranteed each member at death multiplied by the number insured (1000×$1100= $1,100,000). This obligation will fall due in an orderly manner, and the company has apparently ten years in which to collect the sum, but as 100 members died each year the actual payments made by the insured to the company will be not 10,000, but only 5500. Each equitable and necessary payment therefore represents the quotient obtained by dividing the amount insured—viz., $1,100,000—by the total number of payments to be anticipated, and it is found that $1,100,000 divided by 5500 equals $200. This sum is the *premium* or annual payment to be required of each member to pay *death losses.* The company would collect, therefore, the first year from each member $200 ($200×1000 or $200,000) premium, and pay out to the beneficiaries of 100 deceased members $110,000 (100×$1100), leaving a balance of $90,000 to be put aside for reserve. The second year's income from the 900 survivors would be $180,000 and deducting, $110,000 in death losses would leave for that year $70,000, which with that of the first year would give a total excess collection equal to $160,000, but at the beginning of the sixth year it would receive but $100,000 in premiums with which to pay $110,000 of death losses, and from this time on the accumulated reserve of the first five years would be required to meet the deficit created by the shrinking premium receipts of the later years. As equality of age and of the amount insured is here assumed, it is evident that at the end of the tenth year the company could exactly discharge its obligations.

The "*insurance cost*" of any year is the sum obtained by dividing the death losses of that year by the number of men living at the beginning of the year; for example, the losses of the first year $110,000, divided by 1000, gives $110 per man as the actual cost for the first year. In the sixth year losses are the same, $110,000, the number of men paying only 500 ($110,000 divided by 500 equals $220), and it is evident that the actual cost per man has doubled. In every group the cost steadily increases from year to year by reason of the aging of the lives at risk, and the accumulated balance of the first years of low cost forms "the reserve," which is relied upon to secure the payment of the losses of the later years of excessive cost. In actual insurance the problem is more complicated, although the principle remains the same. Thus: (*a*) *The premium must be loaded to cover cost of operation.* (*b*) *The policy holders will be of varying ages.* (*c*) *The reserve will be accumulating and compounding interest.* (*d*) *The yearly increase in new members will materially modify the proportionate gross death loss, although in the whole group it does not actually affect or modify the mortality rate for each age.*

It is evident that although a thousand different forms of policies be presented, the basis for each and every one must be the same, and that the cost of insurance must depend upon (*a*) the ratio of *death losses* to the tabular rate assumed, (*b*) the *interest earned* upon invested funds, and (*c*) the *actual cost of operation. If these points were borne in mind by men seeking insurance they would be saved much misapprehension and disappointment.* The best check upon any company is found in its dividend returns to policy holders, and in the case of the annual dividend policies the insurer is never in ignorance concerning this point, whereas, under the system of deferring dividends for periods of years he has little or no check upon the company's management until the final returns are made.

"*Limited payment*" *policies* are simple life policies carrying a premium so increased as to permit all payments to be made within a specified term of years, ten, twenty, or thirty years, as the case may be, and thus suit the convenience of many who wish such obligations to cease after a certain period. "*Limited term*" *policies* insure the individual for a specified term of years, and usually provide for an extension at the end of the term if desired, providing the insurer pays an increased premium corresponding to his then attained age. As the original premium is relatively small, they often serve a useful purpose and probably represent the least profitable form of policies that a company issues.

Policies may also be either "*participating*," *i. e.*, entitling the insurer to dividend returns, or "*non-participating*," in which case no dividends are paid. The "*endowment*" policy is issued under various forms and covering various periods. It provides not only for the payment of a stated sum in event of death, but of the same amount if the insurer shall be alive at the end of the insurance term, thus introducing a savings bank feature and leading to a decided element of self-selection, inasmuch as the man who is willing to pay the large premium required is, in a sense, betting upon his own good health and constitutional vigor. That this is true is shown by the records of all insurance companies, which show a relatively low rate of mortality among this class of insurance.

Policies may furthermore provide that at death a certain sum considerably less than the face of the policy shall be paid in cash, or, at the option of the beneficiary, a larger stated sum shall be paid in annual instalments for a term of years or as an annuity. With these various forms of insurance as a basis, it will be readily seen that an endless number of combinations may be devised, which, offered under attractive headings, make the work of the solicitor lighter. In none of these are the essential features in any way changed unless the "*tontine*" feature is introduced. This latter is a survival of the ancient gambling spirit upon which modern life insurance has actually been founded, but from the uncertainty and injustice of which it has almost wholly escaped.

Importance of Medical Selection.—By means of the various well-known tables representing the expectation of life an actuary can forecast the number of deaths that will occur in a group of insured lives during any year of insurance, *provided that these lives have been properly selected from a medical standpoint.* The importance of medical selection was not fully recognized until the latter half of the nineteenth century, although credit is to be given to the Equitable of London (1762), which represented the best insurance selection up to the organization of American Life Insurance

Companies. From selection by a lay board of directors without physical examination, the requirements steadily advanced, chief medical officers were appointed, and applicants admitted only upon the recommendation of medical men. In 1867 the Mutual Life Insurance Company of New York established a system of medical referees, who nominated examiners for their respective localities.

This was a great step in advance, and for many years increased care was observed in selection of risks, but of late a custom has become quite general in the United States which tends to vitiate the selection and unduly favor the solicitor, the ultimate decision in doubtful cases being thrown into the hands of a committee, made up in part of laymen, who occasionally have a decisive majority. Its effects vary greatly in different companies, but in general it is a step in the wrong direction and adversely affects the selection.

Efficiency of Medical Selection.—While the present system has proved of the utmost value, it is far from perfect, as is shown by the early deaths from tuberculosis, heart disease, etc., occurring in the experience of every company. For its defects the examining physician must be held chiefly accountable, inasmuch as his representation of the case forms the basis of the home office's acceptance or rejection so far as physical condition is concerned. In a lesser degree it is due to the constant pressure exercised by the purely business end of the home office and by the deficient medical report blanks. The author had occasion to point out several years ago that few companies inquired as to the condition of the pupils and knee-jerks, and, what is still more extraordinary, failed to demand that the temperature be taken. A majority of the blanks recently reviewed still omit these important matters. Indeed, there are a few companies which do not demand a urinary examination unless the amount of insurance sought is above a certain fixed sum or the applicant beyond a certain age.

The chief effect of medical selection falls upon the first five years of insurance, *but it acts throughout the whole term.*

The Organization of a Medical Department.—The medical department at the home office of a company should consist of a medical director and such assistants or associates as are required according to the amount of business. In the larger companies these medical men are usually taken entirely out of practice and give their whole time to the work of the insurance office. It is doubtful whether the service rendered is as good as would be the case if they were to retain a certain amount of office practice, or at least a hospital service, but the arrangement best suits the executive requirements, and will probably be a permanent one.

As medical reports reach the office from the medical examiners they are entered upon a register, and to ascertain if the man has ever had an application modified or rejected by another company, a careful check is made of the interchanged rejection records, which are contained in a card index, advices for which are furnished at stated intervals by a central bureau to which the leading companies report. The blank is then carefully reviewed in order that clerical errors may be detected, and is then turned over to the medical department, where straightforward cases are rapidly passed upon by the assistants, who set aside doubtful reports for further action at the hands of the medical director, or the committee if there be one. The final action taken is then recorded in the register, which should also show the policy number for policies issued, and the rejection number for rejections or modi-

fications made. As a matter of convenience, all modifications or rejected applications should have a separate record book or card index.

The Examining Physician.—The examining physician must be one of record at the home office, and a few companies very wisely demand that examinations be made by the senior examiner in any city or suburban district, and that in event of another being employed a full explanation of the agent's action be submitted with the application. This removes one of the most serious dangers in home office work, viz.: that insurance applicants will be taken to the most careless and slipshod of the medical appointees. Inasmuch as the rigid rule is seldom observed, this constitutes one of the most serious defects of medical selection, as the author well knows from personal observation.

Medical Inspectors.—Medical inspectors should be had wherever possible; they should cover certain specified districts, keep in touch with the insured, be prepared to investigate doubtful cases, and keep close tab upon the medical examiners, as a certain number of men are sure to degenerate during a term of years, and new men will be needed to fill their places. The *death claims* should be referred to the medical department for careful review, and an analysis of such claims entered in a proper record book gives most valuable information in later years.

The Medical Director.—The medical director is ordinarily a much tried man, having to fulfil the difficult function of protecting the company's interest from the standpoint of safety without doing injustice to an applicant and with due regard to the rights of the solicitor and the examiner.

He is usually eminently fair and judicial in his decisions, being removed from all possibility of personal bias or sympathy, and thoroughly equipped from the medical and sometimes from the statistical point of view. The question with him is not as to the effect of admitting an individual risk, but as to the wisdom of permitting the one doubtful risk to become one of a large group, which may furnish a heavy mortality. His attitude is broader to-day than it has ever been before, and founded upon a greater fund of accumulated statistical knowledge than was available a few years ago. His medical judgment in itself must be keen, his powers of observation acute, and, indeed, he seems sometimes to be possessed of a sixth sense, which leads him to suspect under a fair exterior a danger which proves real upon investigation.

The Medical Examiner.—None but thoroughly qualified medical men should be permitted to pass upon an applicant for life insurance, for it requires a thorough training in diagnostic technique, excellent prognostic ability, a far-reaching knowledge of etiological factors, and an ability to prove a man healthy or diseased in the absence of a frank case history, and oftentimes in the face of deliberate misrepresentation. An examiner should have the personal qualities of courage, incorruptibility, firmness, decision, shrewdness, and tact. It is his function to prove or disprove the statement that the applicant before him is in good health, a problem exactly the reverse of that of the physician in practice. Hence he must be well grounded in that much neglected branch of knowledge which deals with the signs of health as well as that relating to evidence of disease.

It seems to the writer that insurance companies should expect of their applicants *average good health*, not "*average health*," unless, as in the case of the English companies and a few American companies, special ratings are made to cover impaired lives. It is too frequently assumed that "average

health" represents the standard, for this might certainly be an extremely low one. The *insurance normal* should mean the promise of a long life, and anything short of that be covered by special policy forms or actual substandard ratings.

In any event, so far as the medical examiner is concerned it is his function to furnish the home office with *all obtainable facts* in relation to the given case, for his opinion as to the insurability of the case may or may not be of great value, this depending upon the extent of his knowledge of life insurance problems. *Most of the rejections made in the insurance office are, as a matter of fact, made by the medical director in the face of a favorable report made by the medical examiner—this is without the slightest reflection upon the honesty or capacity of the local physician, but because of a wider knowledge of the effect of a reported impairment upon the mortality of a large group of individuals of the same type.*

The clerical work connected with the filling out of the blank should be thoroughly and completely performed; *ditto marks* should not be used; no blank space should remain unfilled; *the report should be written in ink and by the examiner himself;* and if facts likely to affect the standing of the risk are brought out, the examiner should always consider carefully the advisability of a notation further explaining their character, and *giving such information as he himself would like to have were he to review the case at the home office.* He may rest assured that the medical director will take nothing for granted, and will save much correspondence by primary notations.

All *corrections* must bear the examiner's initials, and the date of the paper should in every case be the actual date of the examination. American companies demand that no physician shall examine a relation or any person in whose acceptance he has a pecuniary or unusual interest. *He cannot act as solicitor and examiner, nor participate in any agency commission. Examinations must be made in private,* save that the mother or a female friend may be present in the case of unmarried women. A *temporary indisposition* on the part of the applicant invariably postpones the examination, and all *rejections* made or unfavorable opinions given should be recorded by the examiner in a special book and reported to the home office. In the case of long drives or special service he should make his arrangements with the agent for *extra compensation,* otherwise fees are paid by the home office in nearly every case.

In the case of American companies the medical blank is ordinarily forwarded to the home office *by the solicitor,* and this bad practice is excused on the ground that the average examiner will greatly delay the reports, and that clerical or other errors are so frequent as to need the scrutiny of the solicitor to prevent unnecessary correspondence. Whether this is true or not, the examiner should in such cases omit from the blank matters of a delicate or confidential nature, reporting them at once to the home office by mail. *Such communications are held as strictly confidential by all well-organized companies;* indeed, agents are seldom informed as to the cause of rejection, and, unfortunately, this is also the rule in regard to the examiner. Its first application is a good one, but the examining physician would give better service if he were fully advised in confidence as to the causes leading to the rejection of applicants examined by him.

Examiner's Obligation to the Agent.—Prompt and expeditious examinations, a reasonable degree of accommodation, courtesy, and fair dealing are

indispensable. Insurance applicants must, as a rule, be given preference over an ordinary patient in the consulting room, and a physician is often obliged to make an examination outside of his office and perhaps at an inconvenient hour. Every insurance solicitor knows the value of quick action in closing a contract, and the physician should assist him by a prompt response. Beyond this the solicitor has a right to demand thorough and careful work and the making of a full, complete, and *clerically accurate* report, both in his own interest and in that of the applicant. The examiner who is constantly making omissions, forgetting his measuring tape, failing to explain matters that are susceptible of explanation, etc., is not fit for his work.

Examiner's Duty to the Applicant.—The applicant is entitled to a thorough examination and a fair and complete presentation of all facts affecting his insurability. The safety of the company must ever be the first consideration, but the examiner should be careful to give the applicant the benefit of all favorable factors, and to avoid a hypercritical attitude and the use of ambiguous statements of any kind. Once rejected, any applicant will find great difficulty in securing insurance, even although the original refusal was due to the examiner's error. Such mistakes are, however, rare, the company being the usual victim of error and superficial work. The personal friend, the prominent citizen, and the old patient must be treated in every respect as if they were total strangers, and in such cases the courage and tact of a physician is put to the crucial test.

The Application and the Medical Report.—An applicant must make a declaration regarding health, habits, and other matters affecting his insurability, and this is supported by the medical report of the physician. The declaration or application proper is signed by the applicant and witnessed by the physician, and the former should invariably be asked to read the clause inserted at the bottom of the application sheet, as it often contains matters of vital importance to his policy. The medical report is, of course, signed by the physician himself.

Taking the average form as used by American companies, the questions will run about as follows:

1. **Full Name and Address.**—This needs no special comment, save that an especially careful examination should be made in the case of a non-resident. The risk will certainly be thoroughly investigated by the company's inspectors, as many a bad subject seeks a stranger for his examiner because his disabilities are too well known to his local medical men.

2. **Place of Birth.**—This determines the race of the applicant, and it should be remembered that *negroes* are rarely insured, because of their tuberculous tendency and irregular habits of life. The *Mongolian* is also seldom insured, because of difficulty of identification, the unhygienic life led, and the frequency of opium addiction. In general, it may be said that the *English* should be examined with special reference to the condition of the circulatory organs and kidneys, and the existence of, or inherited tendency to, gout; the *Hebrews* with special reference to diabetes and functional nervous troubles, and with the knowledge that they are exceptionally free from tuberculosis. Furthermore, it has been shown that the *Germans* are good risks when insured in early life, indifferent ones at higher ages. The insurance of the *Irish* born applicants who have emigrated to America has proved unfavorable, but this is probably not a matter of race, but related to other conditions.

3. **Date of Birth.**—The age is important in many ways: *it determines the premium rate,* bears a direct relation to probable disease incidence, and, furthermore, applicants under eighteen or over sixty-five are usually refused under straight life plans. The apparent age as relating to the date of birth given is of immense importance. There are many who deliberately understate their age; there are "old young men" and "young old men," the former being bad risks at ordinary rates, the latter exceptionally good ones. *Rapid aging* is one of the surest signs of progressive degeneration of the vascular structures, and should receive careful consideration. The loss of weight, color, and vigor are usually associated with hardened arteries, and followed in a few years by definite evidence of organic disease. Such men are especially likely to *seek* life insurance, and too often obtain it.

Age in connection with family history is also important, certain families tending to die of the middle age diseases, certain others of those of early life. It also bears a relation to weight. In general, companies have experienced a heavy loss on young lives as compared with those of middle age, in spite of the many difficulties attending the selection of the latter.

4. **Residence.**—Certain companies still continue to draw rigid geographical lines in the acceptance of risks, certain others, and notably the English companies, extend their boundaries to cover the larger part of the civilized world, but charge extra premiums on account of residence in certain regions. Under the more rigid restrictions of certain American companies a policy holder must secure a permit even to *travel* in notoriously unhealthy localities. Inquiry is often made as to *changes of residence or occupation* on account of health, and the question is of importance as frequently revealing a past tuberculosis or nervous breakdown. In many localities arrested tuberculosis is exceedingly frequent among the inhabitants, this being especially true of climates deemed favorable to its cure. Indeed, in such localities the altitude may be such as to have so distended the lungs as to completely obscure the signs of extensive past tuberculous lesions. One or two companies ask whether there exists any association with consumptive individuals in actual residence or business, or whether these conditions have ever existed, and if so, when and for how long a period.

5. **Occupation, Past and Present.**—This topic is too large for adequate presentation in this brief article, but in general one must consider: (*a*) *Occupation as related to sanitary environment and exposure to heat and cold.* (*b*) *Occupational poisoning.* (*c*) *The moral hazard involved.* (*d*) *Mental strain.* (*e*) *Occupational neuroses* in connection with occupation, age, habits, previous health, physique, and family history play a part. (*f*) *Liability to accident.*

(*a*) *Sanitary conditions.* The occupants of sweat shops, badly ventilated factories, and crowded, dark, and dirty rooms are bad risks. Many occupations involve the inhalation of dust, as in cotton or flax mills and in pottery works, and to these may be added the risks of an excessively hot moist atmosphere. The hours of work should also be considered. Steel grinding under the old dry method was especially deadly, and still constitutes an excessive hazard, the workers being especially liable to pulmonary diseases. Millers show the same tendency, as do bone and ivory workers and employees of brush, hat, woollen, and fur manufacturers. Stokers, employees of sugar refineries and gas houses, certain grades of iron workers, and bakers suffer from excessive heat and the sudden changes from an indoor to an outdoor temperature.

(*b*) *Arsenic* is conveyed by fumes or dust in milling, grinding, or smelting, and affects workers in cheap wall papers, aniline dyes, toy coloring, shot making, lithography, artificial flower making, the dyeing of woollen goods, and even taxidermists and the makers of playing cards. *Bromine* and *iodine* workers are bad risks. *Aniline* combines its own risk with that of arsenic and nitrobenzol. *Mercury* affects the workers in mines and smelters and the users of acid nitrate and mercury in felting. *Lead* affects those handling it in smelting, refining, and rolling, also makers of type, shot, lead pipe, lead toys, lace, artificial flowers, cheap wall papers, flint, glass, brass instruments, files, litharge, red and white lead, plumbers, typesetters, painters, lacquer workers, bronzers, glaziers, enamellers, glaziers of pots, pans, cardboard, and brick, etc. *Phosphorus:* Occupational phosphorus poisoning is rare and largely limited to workers handling parlor matches. *Copper, bronze*, and *brass* may cause poisoning in copper sheet scrapers, bell metal workers, pin makers, and those similarly occupied. *Chromium* may cause poisons in photographers, stainers of glass and porcelain, banknote printers, and dyers. *Chlorine* is a respiratory irritant, and affects those employed in bleaching processes of various kinds. *Carbon-bisulphide poisoning* is chiefly observed in rubber workers or those using the substance in chemical processes. *Turpentine* may cause disturbance in painters or others who inhale the fumes in unusual quantity.

(*c*) *Moral Hazard.*—The moral hazard and physical impairment of certain occupations are often blended. The brothel keeper, prostitute, gambler and convict, the bartender and saloon keeper are declined insurance, although the two latter classes may be accepted under increased rating in companies insuring impaired lives. In the case of publicans, English companies add from 10 to 15 per cent. as an extra, or somewhat less on endowment policies, but would probably do well to add still more. The greatest care should be observed in insuring wholesale liquor men, brewers, distillers, and hotel proprietors, and they should receive ordinary rating only when total abstainers and having a clean record. Even persons handling bar supplies, mineral waters, and similar articles are constantly exposed to temptation, and frequently become habitual drinkers.

(*d*) *Mental Strain.*—The utmost care should be observed in the examination of those who have been exposed or are at the time liable to severe mental strain or violent or depressing emotions. Executive officers of great properties, speculators, managers of great estates, those laboring under financial embarrassment, and such as work excessively long hours and decline rational exercise and relaxation are oftentimes most dangerous risks.

(*e*) *Occupational Neuroses.*—Few of the ailments coming under this heading have any importance in life insurance rating. Certain affections, particularly the occupational forms of laryngitis, such as clergyman's sore throat or that of the auctioneer, huckster, military officer, or public speaker, should receive consideration in view of the fact that habitual hoarseness is ordinarily a bar to the issuance of an insurance policy, and an injustice may be done if the occupational factor is not considered in such cases.

(*f*) *Risk from Accident.*[1]—The following table will show the ratings adopted by some of the large American companies in this connection:

[1] In a few instances sanitation, moral hazard, etc., enter into the rating.

RULES OF ACCEPTANCE AND EXTRA RATES PER $1000 OF INSURANCE.

Not Accepted:

Acidmakers.
Actresses.
Aëronauts.
Aniline dye workers.
Arc-light trimmers.
Asbestos workers.
Ash-pitmen.
Athletes, professional.
Barkeepers.
Baseball players, professional.
Battery men.
Beer bottlers.
Bicycle riders, professional.
Blasting, employees engaged in.
Bleachery workers.
Bookmakers, races.
Brewers.
Brewery employees.
Bridge builders, employed on large iron structure.
Button makers.
Caisson workers.
Carders, cotton and woollen mills.
Cartridge makers or loaders.
Cement mill employees.
Coalminers.
Commercial travellers selling liquors, cigars, bar supplies, mineral waters.
Cutlery grinders, finishers, or polishers.
Day laborers.
Deputy sheriffs.
Detectives.
Dippers in potteries.
Distillers.
Distillery employees.
Divers.
Electric light employees.
Explosives, makers and handlers of.
Filecutters, grinders or finishers.
Firemen, in large towns or cities.
Fireworks, makers and handlers of.
Flintmill workers.
Glass factory employees, except office.
Glass gatherers.
Glassblowers.
Glasscutters, grinders and polishers.
Grain elevator employees.
Grinders of edged tools.
Grinders of lenses.
Horsetrainers and handlers.
Hotel proprietors. Full particulars must be submitted to the home office.
Hotel proprietors tending bar.
Illiterates.
Indigo workers.
Jockeys.
Lime workers.
Linemen, telegraph and telephone.
Liquor dealers.
Lumbermen, in woods or mills.

Not Accepted:

Marble- or granitecutters.
Matchmakers.
Miners, except superintendents and office men.
Mirrormakers.
Mixers in potteries.
Oilers, cable roads.
Oil-well shooters.
Plaster-of-Paris workers.
Policemen.
Privates and non-commissioned officers.
Quarrymen.
Railroad employees—
  Brakemen, freight or mixed.
  Conductors on freight or mixed.
  Flagmen.
  Switchmen.
  Wrecking-train employees.
  Yard men.
Sailors.
Saloonkeepers.
Sawyers.
Scavengers.
Scourers in potteries.
Sheriffs and deputies.
Smelters, employees.
Submarine workers.
Sweepers in potteries.
Turkish-bath employees.
Welldiggers.
Zinc work employees.

No Extra:

Railroad employees—
  Conductors on passenger train, despatchers.
Waiters.

Extra:

Bakers' employees, 10 or 15 payment life, or 10, 15, or 20-year endowment.
Bridgebuilders, employed on ordinary short iron or wood structure, $10.00.
Celluloid workers, $10.00.
Commercial travellers, depend upon line of goods handled.
Domestics, $5.00.
Electrical engineers, $10.00.
Electrical railway conductors and motormen, $5.00.
Emery grinders, $5.00.
Firemen in large cities—
  Chief, $5.00.
  Assistant chief, $7.50.
Fishermen, professional, $10.00.
Ground layers in potteries, $5.00.
Hatters' employees, $5.00.

Extra:
- Iron and steel workers, subject to extreme heat. Full particulars must be submitted to home office. Undesirable at best.
- Mining superintendents, $10.00.
- Navigators, merchant marine—
  - Bargemen, $10.00.
  - Boatmen, $10.00.
  - Firemen, $10.00.
  - Officers or engineers, $5.00.
  - Petty officers, $10.00.
  - Raftsmen, $10.00.
- Painters (house), $5.00.
- Railroad employees—
  - Brakemen, passenger, $5.00.

Extra:
- Railroad employees—
  - Baggagemasters on train, $10.00.
  - Engineer, passenger, freight, or mixed, $7.50.
  - Express messengers, $7.50.
  - Firemen, passenger, freight, or mixed, $10.00.
  - Postal clerk, $5.00.
  - Section foremen, $5.00.
  - Section hand, $10.00.
  - Yard superintendents, general, $7.50.
- Riggers, $5.00.
- Roofers, $10.00.
- Slate roofers, $10.00.

6. **Affirmation of Good Health.**—"Are you now and usually in good health?" is a question generally asked of an applicant. This is extremely important, and were it answered truthfully in all cases would go far to protect the company from bad risks; but, as a matter of fact, the average applicant for life insurance, however truthful he may be in other relations, is inclined to forget or minimize any matters that might affect his eligibility for insurance. It would seem that the temptation to suppress vital facts in the interest of the family members, who are to benefit by insurance, is too great, and again and again men of the highest standing in the community will misrepresent their past and present health and be proved falsifiers by the report of confidential agents of the company.

7. **Have You Been Successfully Vaccinated?**—Aside from the affirmation of vaccination, the examiner is requested to satisfy himself as to the presence of the scars indicating efficient vaccination and the date of primary and subsequent vaccination scars. American companies too largely disregard this requirement, which ought to be insisted upon, if for no other purpose than the promotion of public health.

The following conditions are subject to direct inquiry:

1. **Abscesses.**—The acute or chronic nature, severity, duration and location of abscesses and their resulting scars should be carefully noted. In the groin they are usually due to venereal disease or psoas abscess; about the rectum to fistula; on the legs to syphilis, tuberculosis, or varicosities; and in the cervical triangle, spine, and larger joints to tuberculosis.

2. **Appendicitis.**—Direct inquiry under this head may yield nothing and the condition come to light under the patient's diagnosis of "bowel trouble," "constipation," "inflammation of the bowels," "colic," "indigestion," "stoppage of the bowels," "peritonitis," or "typhoid fever," and oftentimes the examiner must make his own diagnosis from a review of the symptoms presented. The disease is extremely important to life insurance companies, 5111 deaths from appendicitis and 7501 from peritonitis being reported as occurring in the United States in one year. It is probable that at least 10,000 and more likely 15,000 die annually from this cause. It chiefly affects the younger policy holders, and thus furnishes a disastrous form of mortality.

No examination will eliminate a future primary appendicitis, and the insurance problem covers the treatment of cases in which it has occurred. The following classification represents a careful and thorough investigation

of the subject on the part of the writer:[1] Treatment under which recovery has taken place:

Group A. *Medical.* (1) *Catarrhal.* (The only cases properly belonging to the medical group.) (2) *Suppurative. Suppuration with spontaneous rupture into bowel. General peritonitis (recovery extremely rare).*

Group B. *Surgical.* (1) *Complete removal of appendix without drainage.* (2) *Complete removal, with drainage of an abscess cavity.* (3) *Drainage without removal of appendix.* (4) *Removal of appendix in cases of spontaneous rupture into bowel complicated by dense adhesions.*

Postoperative complications: (1) Intestinal obstruction. (2) Persistent pain and tenderness. (3) Ventral hernia. (4) The nephritis due to anesthetics. (5) Fistula.

(1) *Sex.*—It was formerly supposed that four times as many men as women suffered from appendicitis, but the opinion is rapidly gaining ground that it is far more frequent in the female than was formerly supposed, many of the acute inflammations hitherto charged to the pelvic organs proving to be primarily due to appendicitis.

(2) *Occupation.*—Violent exercise, particularly when associated with cold and dampness, is often a factor in producing an attack of this disease, and this is particularly true of those who are not accustomed to hard physical labor.

(3) *Intestinal Tract.*—Intestinal indigestion and constipation undoubtedly play an important part in the production of the disease.

Statistics as to Relapse.—It is extremely difficult to secure accurate data upon this subject, as may be realized from the fact that the reports of several observers give figures varying all the way from 10 to 50 per cent. of those cases in which the appendix has not been removed. *It is probable that between 50 and 60 per cent. of second attacks occur before the expiration of six months; between 80 and 90 per cent. within one year, and practically all within a period of about two years,* although instances have been reported, and indeed observed by the writer, in which relapse has occurred after twelve or fifteen years of immunity. The suppurative cases in which drainage has been established without removing the appendix are believed by some observers to be safer as regards relapse than the unoperated catarrhal cases.

Spontaneous Rupture of an Abscess into the Bowel.—It would seem that in many respects the natural drainage established by rupture into the bowel is almost as efficient as that produced by the surgeon, but it should be remembered that if a second attack occurs, the operation is complicated by the adhesions. Such cases are undoubtedly somewhat more likely to recur than those treated primarily by operation.

Postoperative Complications.—Fistula.—This is not unusual and is of little importance, because it is almost certain to appear within a few days or weeks after the operation, and, indeed, usually disappears spontaneously. The presence of a fistula should, of course, in any case be reported by the examiner, and would necessitate special rating.

Intestinal Obstruction.—This rare complication follows operation upon suppurative cases, and, like fistula, should make its appearance within a few weeks after the operation, rarely at any distant period.

[1] *The Medical Examination for Life Insurance*, 2d edition.

Ventral Hernia.—This complication is likely to make its appearance within one year, and commonly follows cases in which prompt closure of the wound was not obtained. In itself it is not a condition which materially affects the mortality rate. In some instances no operation is necessary, and if one has to be performed, there is hardly any mortality connected with it.

Nephritis following Anesthesia.—Some surgeons look upon this condition as worthy of consideration, and believe that in rare instances the use of ether as an anesthetic is the starting point for chronic nephritis. Such instances are probably so rare as to make them negligible, but in any event the examination of the urine would eliminate this risk.

Conditions of Acceptance. First of all, in every case in which appendicitis is reported, a careful history of the attack, and the result of a thorough examination should be presented to the medical director. He should report upon the following points:[1] (1) Number of attacks. (2) Dates of the attacks. (3) Their severity. (4) The duration of each. (5) Whether or not suppuration was present. (6) Whether operation was advised or performed, and if so, exactly what was accomplished. (7) Condition of the wound at the time of examination. (8) The presence of any tenderness or muscle spasm upon the affected side. (9) The general health of the patient; whether or not he has recovered his former weight and is attending actively to his business. (10) Condition of the gastro-intestinal tract, with special reference to pain, flatulence, constipation, or diarrhœa. Persistent tenderness following a case in which the appendix has not been removed seems to be a precursor of recurrent attacks.

As regards the actual acceptance of the case, it would seem that the following rules might reasonably be laid down, the applicant being in good health:

(1) Cases of non-suppurative appendicitis in which the appendix has been removed and primary union obtained should be acceptable from three to six months from the time of operation.

(2) Cases of simple appendicitis in which no operation has been performed should be acceptable after a period of immunity from all symptoms varying from two to five years.

(3) Suppurative cases in which drainage has been established without the removal of the appendix should be acceptable after two years of immunity from all symptoms.

(4) Cases of suppurative appendicitis in which the appendix has been completely removed should be acceptable after one year.

(5) Cases of unoperated suppurative appendicitis with spontaneous rupture and bowel drainage should be acceptable after three years' immunity.

(6) Cases in which general peritonitis has been present should be acceptable after one year if the appendix has been successfully removed and health restored; acceptable after five years' immunity and complete restoration to health, if the recovery has been the result of a simple drainage operation. If treated medically, it would probably be safe to demand a period of postponement of not less than five years.

(7) Recurrent cases should have at least five years of complete immunity from symptoms.

In all cases these recommendations are based upon a favorable report

[1] The examiner's omissions in regard to these matters are a constant source of irritation and time-consuming correspondence on the part of the home office.

from the medical examiner, and a substantial extra premium would be necessary if fistula was present at the time of examination. Occupation must materially modify acceptance in all cases where the appendix has not been removed, or where violent exercise may bring an unusual strain upon the abdominal wall. The writer believes that under such rules as have been suggested these cases may be received and granted insurance upon any plan, with justice to themselves and safety to the company.[1]

3. **Asthma.**—The mortality investigations of the Actuarial Society of America have borne out the opinion long entertained by life insurance medical directors that asthma, even in carefully selected and favorable cases, would furnish a high mortality in middle age entrants. Similar cases in young persons have proved much more favorable, inasmuch as cases have seldom been accepted by the American companies unless supposedly cured, and such are likely to remain well. *The opinion sometimes expressed that asthma does not greatly shorten life is proved wholly fallacious.* The history of asthmatic seizures calls for a careful report as to the dates of occurrence, severity, and supposed cause, and for an especially careful examination of the lungs and nasal passages for chronic bronchitis, emphysema, and tuberculosis; of the heart and bloodvessels for aneurism, arteriosclerosis, and valvular or myocardial disease; and of the urine. Tuberculous patients frequently speak of their trouble as an asthma, and the same is true of those having uncompensated heart lesions, chronic nephritis, and aneurism. Most patients, even though reported cured, are rejected under straight life plans or granted policies for short terms. The hay fever asthma is, of course, relatively unimportant, so that if attacks are distinctly proved to be associated with this condition and to occur at no other time the risk is not materially increased.

4. **Bladder Trouble.**—This general question covers cystitis, disease of the prostate, passage of calculi, and dysuria in general. Any existing disability disqualifies for ordinary forms of life insurance. Past ailments must be completely cured and remote.

5. **Colic.**—A most careful report is required as to the symptoms, dates, number of attacks, and probable cause of this condition, and the examiner should consider as possibilities renal and gallstone colic, appendicitis, strangulated hernia, lead poisoning, Dietl's crisis, pylorospasm, locomotor ataxia (abdominal crises), arteriosclerotic abdominal colic, Pott's disease, abdominal aneurism, spastic constipation, mucous colitis, gastric and duodenal ulcer, and ordinary acute indigestion. "Gastralgia" is hardly to be considered as a clinical entity at the present day.

6. **Cough.**—The usual question is, "Are you now or have you ever been subject or predisposed to cough, habitual expectoration, difficulty of breathing, palpitation, or catarrhal disease?" Any chronic cough or even hoarseness will debar an applicant from insurance of the ordinary form, although the question of occupational hoarseness is always to be considered. In describing any past cough, its severity, frequency, and duration should be carefully noted, as should the question of expectoration, coincident loss of weight, change of residence or occupation, dyspnœa, paroxysmal or upon exertion, and the result of any sputum examination if made. By "catarrh" is

[1] The frequency with which a slight rise in temperature occurs in chronic appendicitis emphasizes the importance of a temperature record as a routine measure.

meant any severe or persistent nasal catarrh leading to health impairment, the ordinary forms being negligible. "Palpitation of the heart," so often included in this question, if occurring in young people without evidence of cardiac lesion and only occasionally, is unimportant; if habitual, and especially if occurring in older persons, it is a bar to insurance on ordinary plans.

7. **"Debility" and "Nervous Exhaustion."**—Inquiry under this head frequently develops an important history of previous or existing health impairment, and careful inquiry should be made as to its duration, effect upon the weight, association with fever, the treatment pursued and for how long a period, and in what institution if any it was carried out. It may be a trivial or temporary indisposition, cover an actual physical or nervous breakdown, or even represent past insanity, alcoholism, or drug habit.

The writer's personal experience would indicate that *relatively* few cases of pure neurasthenia occur, nearly all coming under his observation being associated with recognizable ailments often serious, although usually curable. Among the unrecognized factors in cases which had been previously pronounced "neurasthenia" he has found gastroptosis, gastric and duodenal ulcer, chronic severe anæmias, incipient chronic nephritis, valvular heart disease, chronic myocarditis, and early pulmonary tuberculosis. The neurasthenic patients doubtless invite a hasty and superficial diagnosis which is often seemingly confirmed by their response to the ordinary treatment, which includes the rest and improved nutrition so valuable in nearly all chronic organic ailments.

8. **Delirium.**—This may remind the applicant of an attack of delirium tremens or merely serve to bring to light some severe illness of the past.

9. **Diabetes.**—A history of glycosuria will almost invariably mean the rejection of the applicant under ordinary forms of life insurance. It occasionally happens that an excessive amount of glucose may have been ingested before the examination, but unless this should have exceeded 100 grams the case is rendered no better, as that amount should be taken care of by the normal organs. As it is almost impossible to distinguish dietetic or lipogenic diabetes from true diabetes in insurance applicants, because of the readiness with which deceptive disappearances of the sugar may be brought about by diet and drug administration, any trace of sugar must be held as calling for rejection or special rating.

10. **Diarrhœa and Dysentery.**—Ordinary trivial diarrhœas, unless frequent, are unimportant, but chronic diarrhœal or dysenteric attacks call for rejection of the risk or insurance under special rates. Not infrequently cancer or tuberculosis is regarded and reported as dysentery by an applicant.

11. **Dysuria.**—Aside from the previous question covering bladder trouble, specific inquiry should be made as to whether there is any difficulty in passing water, and as to whether the applicant rises at night to pass it. Diseases of the prostate gland, interstitial nephritis, chronic cystitis, and diabetes are the conditions usually associated. The statement that it is a habit may be true, but such a habit is rare.

12. **Dizziness.**—Persistent or frequently recurring vertigo should prevent insurance upon the ordinary plan during its continuance, and be regarded with special suspicion when occurring in elderly people. It suggests questions as to sexual, alcoholic, and tobacco excess, or the drug habit, and may be due to weak heart, anæmia, errors in refraction, arteriosclerosis, or, in its

lighter forms, to indigestion, neurasthenia, etc. It is frequently associated with past apoplectic seizures, arteriosclerosis, extreme anæmia, Bright's disease, exhausting illness, and more rarely with Ménière's syndrome.

13. **Dropsy.**—Any existing œdema, aside from so-called angioneurotic œdema, calls for rejection of the risk or special rating, and suggests a careful examination and inquiry relative to heart disease, Bright's disease, severe anæmia, sclerosis of the liver, varicose veins, and in general, diseases associated with marked cardiac weakness or circulatory obstruction. If occurring in the past, it necessitates a most careful inquiry. Occasionally, when denied, it may be suggested by the presence of striæ upon the surface of the abdomen or over the hips.

14. **Drug Habit.**—The applicant is asked, "Do you now or have you ever habitually used morphine, chloral, or cocaine?" Such a question is almost invariably answered in the negative, and many of the victims of the drug habit, and especially of the cocaine habit, are unaware of their addiction. The examiner is therefore obliged to depend upon the physiognomy, manner, and such other indications as may be available. Pinpoint or unequal pupils or marked pupillary dilatation may prove suggestive. In some instances the sallow, inelastic skin and coated tongue, nose rubbing, and emaciation may suggest morphinism, although often the face appears puffy and bloated. In cocainism pupillary dilatation is likely to be marked, the mental condition is suggestively unstable, the pulse weak, irritable, and often irregular, and there may be dark rings about the eyes. The discovery of hypodermic punctures, usually with infiltration areas, is of course pathognomonic, and most morphine users employ the subcutaneous method. Cocaine takers, on the other hand, often acquire the habit by the use of nasal douches and sprays, and may employ no other channels for the ingestion of the drug. Any habitué should be considered uninsurable, and in the case of a past cured habit the time of probation should be long, and even then an extra premium rate is necessary.

15. **Dyspepsia.**—Trivial, infrequent attacks of dyspepsia are not important in insurance acceptance, but chronic disease impairs the life and demands rejection under ordinary policy forms. In any event, the most careful examination is requisite to insurance even under extra rating. The question of associated disease must always be considered, among the conditions being heart disease, Bright's disease, tuberculosis, and primary gastric lesions, such as dilatation, ulcer, and malignant disease. Careful inquiry as to loss of weight, presence of pain, etc., should always be made.

16. **Erysipelas.**—A remote single attack of erysipelas is unimportant; recurrent attacks should disqualify for ordinary forms of insurance.

17. **Fainting, Loss of Consciousness.**—Under this head must be considered uræmia, epilepsy, minute apoplexies, hysteria, anæmia, and heart disease, as well as ordinary and relatively trivial syncopal attacks. Any history of recurrent seizures of this kind, unless far in the past and entirely recovered from, impairs the life.

18. **Fistulæ or Open Sores.**—Any open sore of whatever nature disqualifies the applicant for ordinary insurance during the term of its continuance. In the case of fistula-in-ano, if it be remote and entirely cured, and the applicant be physically sound and lacking a family history of tuberculosis, acceptance is justifiable, otherwise special rating or absolute rejection is required. The lesion is frequently not reported or discovered during the examination, and may represent not only tuberculosis, but carcinoma, or,

more rarely, prove to be merely an inflamed pile or an anal fissure. Chronic ulcers of any description are the subject of special rating, and must be individually passed upon.

19. **Fits, Tremors, and Convulsive Seizures.**—The first term is used on account of its being readily understood by any applicant, but he should also be interrogated concerning "convulsions," "cramps," or "spasms," and tremor itself is a matter for the examiner's observation. Persons who have had chorea are uninsurable unless it is remote and they are without cardiac lesion, although in the latter case in later years they may be rated much as other similar lesions would be under special policy forms.

Epilepsy should make its possessor uninsurable; past cerebral hemorrhage calls always for rejection or in rare instances permits special rating. Uræmic convulsions occurring during a *remote* attack of acute Bright's disease may be disregarded; otherwise they indicate an uninsurable condition. *Cramps* in the calves of the legs are usually an indication of serious degenerative organic disease, such as that due to alcoholism, lead poisoning, diabetes, or Bright's disease, but the attacks directly following severe overexertion are unimportant. *Tremor* if increased by purposeful movement, as buttoning or unbuttoning a collar or coat button, *suggests* disseminated sclerosis. A fine rapid tremor is well known as a symptom of alcoholism or exophthalmic goitre. The tremor of paralysis agitans is associated with the mask-like countenance, and usually with general stiffness of movement. This disease is one of long duration, is not likely to be met with by the insurance examiner in its advanced form, and if seen early may permit the issuance of very short term endowment insurance or special rating. Hysterical tremor is associated with other signs of hysteria.

20. **Glandular Swellings.**—Actual and existing glandular enlargement, unless merely residual and related to a past cured ailment, demands a painstaking examination as to the primary cause, and usually means the rejection of the applicant. The question of scars as indicating past glandular inflammation has been discussed under abscess. The examiner must have in mind, as possible causes of glandular swelling, syphilis, tuberculosis, Hodgkin's disease, leukæmia, chancroid, gonorrhœa, and simple adenitis. Glandular swelling may be present in the neighborhood of old ulcers or the seat of any suppurative process.

21. **Gout.**—True gout markedly impairs the life, and its possessor is not insurable under ordinary policy forms. English companies accept favorable cases with five years addition usually under an endowment terminating in middle age, as the death rate is especially heavy between fifty-five and sixty-five. On whole life the rating should be quadrupled. Excessive weight, the history or presence of glycosuria, and occupation or habits suggesting the overconsumption of alcohol, should demand rejection. Many of these individuals seek insurance in middle age, and those accepted yield a high mortality after the first five years of insurance.

22. **Headaches.**—The following causes of headache must be considered and investigated if the condition is admitted by the applicant as frequent or persistent: Anæmia, auto-intoxication, nephritis, cerebral congestion, carious teeth, chronic mineral poisoning, chronic otitis, disease of the brain in general, brain tumor, dyspepsia, eyestrain, gout, nasal catarrh, nervous headache, "migraine," neuralgia, syphilis, uterine or ovarian disease. The question of seat of pain, character, severity, and persistence, the presence of local tenderness, the hour at which it comes on, duration, frequency of

recurrence, associated symptoms, and hereditary tendency should in every case be investigated.

23. **Hæmoptysis.**—"Blood spitting," if admitted, will in 90 per cent. of the cases prove to have been due to tuberculosis of the lungs. Occasionally an overconscientious applicant will report trivial hemorrhages, which are readily placed and eliminated. The question covers hæmatemesis, so that not only pulmonary tuberculosis and aneurism or malignant disease of the throat, but cirrhosis of the liver, gastric ulcer, and carcinoma are included. Coincidently the term "other hemorrhage" is usually introduced, which may bring to light leukæmia, hæmophilia, hemorrhage due to intestinal parasites, or of the bladder or kidneys. Inquiry should be made as to the date or dates, supposed location of the hemorrhage, amount of blood discharge, associated symptoms during the attack, and state of health previous and subsequent to it, as well as the circumstances supposedly inviting or causing it. Not less than ten years' immunity should be demanded following the severer hemorrhages and especially those of the pulmonary type, and no ordinary insurance policy can be issued even then unless the applicant be wholly sound, of unusual physique, favorably environed, and possessed of a clean family history. The collective mortality investigation has shown an enormously increased death loss in young policy holders, and favorable results only in entrants between the ages of fifty-seven and seventy. Early ages and any history of alcoholism are especially unfavorable.

24. **Injuries and Surgical Operations.**—The line of investigation demanded is self-evident, but it is always well to pursue the inquiry with greater care than would be necessary in the case of an ordinary patient. Attempted suicide may stand revealed, as well as falls due to drunkenness or epilepsy, brawls or actual shooting affrays, or an operation may have been undertaken for the relief of malignant or tuberculous disease.

25. **Insanity.**—Any history of insanity should render an applicant uninsurable under ordinary policy forms, and such lives are seldom accepted under any conditions.

26. **Jaundice.**—No case of existing jaundice should be accepted; the history of an attack associated with gastro-intestinal disturbance and a complete and ready recovery from it are of little importance in young persons, but demand a most careful investigation in those of middle age because of its frequent relation to gallstones or chronic disease of the gastro-intestinal tract.

27. **Kidney Trouble.**—A history of acute nephritis in youth, remote and entirely cured, as indicated by good health, and normal urine, is no bar to insurance, and the same is true of pyelitis or the albuminuria of acute infectious disease; furthermore, many applicants report past disease of the kidneys based only upon an excess of phosphates or urates, reinforced oftentimes by a quack's diagnosis.

28. **Use of Liquor.**—The following questions are usually asked: "Use of ardent spirits; extent; average quantity each day?" "Do you use ardent spirits, wine, or malt liquors? If so, to what extent? Average quantity each day?" "Have you ever taken any cure for intemperance?" "Are your habits at present, and have they always been sober and temperate?" "Have you ever used intoxicating liquors to excess?" "Have you ever been intoxicated?"

Although searching, these are often insufficient, as insurance applicants

do not often admit intemperance; the use of general terms, such as "occasionally," "now and then," "take a social drink," "often not for months," and even the terms "very rarely," "have no habit," are not dependable, and may conceal either habitual drinking or, as is often the case, intermittent drinking. *Some kind of an average must be stated,* so many drinks each month or week, and nothing else is likely to prove satisfactory. As to the actual extent of alcoholic indulgence permissible, it is extremely difficult to draw a line, and, as a matter of fact, a positive statement is impossible. The man who drinks a glass of wine at dinner or who takes a little whisky and water on a full stomach may be an excellent risk and may indulge to a considerable extent without harm, whereas his associate who drinks raw liquor at irregular times may be a very bad risk. Everyone knows in a general way the difference between moderation and excess, and it is only the truly moderate drinker or total abstainer who should be granted life insurance. The man who goes on sprees is more dangerous, as a rule, than the steady drinker, and one of the worst of risks is the man who never gets drunk yet consumes a large amount of alcohol daily The "sneak drinker" is occasionally detected, but, as a rule, his weakness is known only to members of his household or employees of hotels and Turkish bath establishments. Special objection exists in the case of those drinkers in whose family history there is alcoholism or one of the hereditary alternatives. Such easily contract a habit and rarely succeed in breaking it.

In any case of past excessive indulgence, total abstinence extending over a period of many years should be required, and Keeley cure graduates, even such as remain cured, yield a tremendous mortality. Regardless of the age of entrants, the condition of the heart, kidneys, bloodvessels, and liver should be carefully determined when doubt arises, and tremor, peculiarity in manner, or the well-known stigmas of alcoholism may prove important.

29. **Lumbago.**—Simple myalgia is unimportant, but one must have in mind the loin weariness of Bright's disease, pyelitis, mucous colitis, sciatica, spinal caries, locomotor ataxia, gallstone and renal colic, and even spastic constipation. Persistent backache is incompatible with a sound state of health.

30. **Nasal Polypi.**—These prevent insurance during their continuance or within a year after renewal, and an examination of the nasal cavity is demanded.

31. **Neurasthenia.**—Any existing neurasthenia should render the applicant uninsurable during its continuance, and even at least two years after its cure a special inquiry should be made as to manifestation, duration, causes, and existing environment at the time of application. The term may cover insanity, alcoholism, and serious chronic diseases, thus necessitating special inquiry as to the institution or hospital in which treatment was applied, and invariably a note of inquiry to the attending physician.

32. **Palpitation.**—Existing palpitation disqualifies, but, generally speaking, occasional attacks are unimportant in young individuals and sinister in older ones.

33. **Paralysis.**—Infantile paralysis need not disqualify in the adult applicant, and the same may be said of facial paralysis, remote, completely cured, and affecting only the nerve trunk. In the former case the deformity may so impair locomotion as to increase the liability to accident, and in the latter form a history of loss of consciousness, vomiting, attendant hemiplegia, ocular paralysis, etc., would disqualify the applicant. Reference to the

attending medical man is always important. Various forms of neuritis leading to temporary paralysis do not affect the risk. Aside from these forms, cases of paralysis are entirely outside the ordinary form of insurance.

34. **Pensions.**—An applicant drawing a disability pension should not be an insurable risk save in exceptional instances, but the laxity of the pension laws of the United States has been such as to reveal frequent instances in which an applicant represents himself to the insurance company as being in perfect health, and to the Government as a physical wreck. In such instances rejection is certainly justifiable.

35. **Physical Defects and Deformities.**—*Amputation* impairs the risk if locomotion is so seriously interfered with as to introduce a marked liability to accident and injury. The writer is not in accord with the general belief of life insurance medical officers that amputations, even although high up, should be held to impair the life, believing that this opinion originated in the days of unclean surgery with its attendant prolonged suppuration, secondary infection, and painful or imperfect stumps. It is probable that in the case of hip-joint amputation a small extra would be justifiable or the applicant should be held to an endowment for a modern term; otherwise, it would seem as if ordinary insurance should be granted in these cases.

Deformities impair the risk according to their cause and degree. Slight lateral curvature is unimportant; extreme curvature impairs the risk. Cured hip-joint disease should never permit insurance at ordinary rates, and the hunchback seldom lives beyond middle age. Deformities from infantile paralysis are unimportant, as before stated. In general, all tuberculous joint lesions, even although cured, make extra rating necessary on account of the danger of recurrence, either in the joint itself or in other regions, and, further, because of the evident loss in vital resistance.

36. **Piles.**—The existence of a severe attack of hemorrhoids, inflamed or otherwise, should mean postponement until they are cured, and the same statement applies to bleeding piles, unless the hemorrhage is very slight and occurs at long intervals. In any such case a rectal examination is imperatively demanded, and may, on the one hand, show an entirely negligible condition, or, on the other, fistula, syphilis, tuberculosis, or malignant disease of the lower intestinal segment.

37. **Pleurisy.**—Unless many years have elapsed and the applicant presents a clean family history and general health record, a history of empyema should demand special rating, and even in the case of ordinary serous pleurisy the family history and physique should be exceptional, and acceptance should not be made within from two to five years from date of recovery. This care is necessary because of the frequency with which pleurisy is tuberculous. The resulting chest deformity is a matter for careful consideration, particularly in connection with empyema.

38. **Pneumonia.**—The exact history of an attack of pneumonia should be elicited for the purpose of identifying the disease, its duration carefully noted, and if there be a history of recurrence a long period of postponement is demanded; otherwise, if an applicant be unexceptionable in other respects, he may be accepted after one year's postponement, although a two years' term is far safer.

39. **Rheumatism.**—Under the prevailing rulings one severe attack of inflammatory rheumatism calls for postponement for at least two years, with complete absence of rheumatic symptoms. Repeated attacks should

mean rejection under ordinary policy forms, but admit special rating, and, indeed, the English companies in many instances add seven years to the age and demand three years immunity from a single attack, and are probably quite right in assuming this position. In all cases it is evident that the condition of the heart and the family history must be a large factor in acceptance, and these cases should be examined with the most scrupulous care. Inquiry should be made concerning any *surgical interference* necessitated, as this often throws an important light upon the original diagnosis, which may have been misquoted by the patient. On the other hand, the term "acute" or "inflammatory" rheumatism is not infrequently applied by the applicant to a negligible condition.

40. **Scrofula.**—This obsolete term is still used in interrogating insurance applicants, and may reveal a history of past tuberculous disease of the glands or bones, of great importance in rating.

41. **Shortness of Breath.**—Any existing or habitual dyspnœa is a bar to insurance, or demands special rating in favorable cases.

42. **Sores.**—This general term may elicit a history of chronic ulcer, suppurative glands, epithelioma, chancroid, and bubo. Any existing open sore, unless of an evident trivial nature, prevents acceptance during its continuance.

43. **Stricture.**—Urethral stricture or any other evidence of active or uncured gonorrhœa demands postponement until recovery is complete.

44. **Sunstroke.**—Even a simple attack of heat exhaustion demands several years' postponement, during which term all symptoms have been absent, even during hot weather. A history of true sunstroke almost invariably demands rejection or a large extra in rating.

45. **Syphilis.**—*The results of investigation of the Actuarial Society of America should put an end for all time to the idea that syphilitics are insurable under ordinary policies.* Short endowment may be granted in favorable cases, and special rating is peculiarly applicable to this class of cases. Even endowment insurance should never be offered except after a period of postponement representing at least five years of complete immunity from symptoms following a course of treatment radical and covering a period of not less than one year, and even then should not carry the risk beyond the age of fifty-five. The remote effects of syphilitic disease as tending to cause degenerative lesions, especially those of middle age, are important, and hence we find that even in the American companies in which every precaution has been taken in the past to select good risks, the results are unqualifiedly bad. On the other hand, every precaution should be taken to protect the applicant from rejection based upon spurious diagnoses, such as are frequently made by quacks for purposes of revenue. Whether the addition of five years at the age of thirty as applied by certain English companies is sufficient may well be doubted.

46. **Tobacco.**—The use of tobacco is ordinarily not a factor in determining insurance. In exceptional instances it may be so excessive as to constitute a hazard, and this may be especially true in the case of elderly applicants. If associated with attacks of palpitation or tremor, it of course becomes of importance.

47. **Weight and Height.**—The following table shows the relation of weight to height. The allowable variation in the case of women upon the overweight side should undoubtedly be greater than in the case of men, but in

general, 20 per cent. underweight or overweight is allowable provided the family history and personal health record are favorable. The Actuarial Society's investigation has merely emphasized what American medical officers have been brought to perceive through disastrous experience, viz.: that too great an allowance upon the side of overweight has been made in the past, and this is particularly true of older entrants. As regards underweight, 20 per cent. is allowable only when the applicant has a family history and personal record free from tuberculosis, and well developed and freely expanding normal lungs. Occupation and physical activity must be considered in this relation, as many a slender man is exceptionally healthy and long-lived. In general, however, the experience with lightweights is unfavorable, and such groups show a high mortality from tuberculosis.

FOR AGE FORTY-SEVEN AND UPWARD.

HEIGHT.	NORMAL WEIGHT.	— 20 PER CENT.	+ 20 PER CENT.	+ 30 PER CENT.
5 feet,	134 pounds.	107 pounds.	161 pounds.	174 pounds.
5 " 1 inch	136 "	109 "	163 "	177 "
5 " 2 inches	138 "	110 "	166 "	179 "
5 " 3 "	141 "	113 "	169 "	183 "
5 " 4 "	144 "	115 "	173 "	187 "
5 " 5 "	148 "	118 "	178 "	192 "
5 " 6 "	152 "	122 "	182 "	198 "
5 " 7 "	157 "	126 "	188 "	204 "
5 " 8 "	162 "	130 "	194 "	211 "
5 " 9 "	167 "	134 "	200 "	217 "
5 " 10 "	172 "	138 "	206 "	224 "
5 " 11 "	178 "	142 "	214 "	231 "
6 "	183 "	146 "	220 "	238 "
6 " 1 inch	188 "	150 "	226 "	244 "
6 " 2 inches	194 "	155 "	233 "	252 "
6 " 3 "	200 "	160 "	240 "	260 "

For younger ages, subtract ½ pound for each year under forty-seven, and the result will be the normal weight for the given age (Mr. Wells). (*The Medical Examination for Life Insurance*, Greene.)

At the opposite pole, but equally dangerous, are the big-bellied individuals who are usually flabby, but given to heavy eating and indolent ways. A family history of tuberculosis in the case of lightweights is no less damaging than the history of apoplexy, heart disease, and nephritis in the heavyweight type. The short endowment policy is especially applicable to the overweight individual, *although within narrow limits*. In every case the applicant should be weighed and measured by the physican. The chest measurement should be taken with a *tightly applied tape*, the abdominal measurement should represent the maximum, and *the tape should not be tightly drawn*. Professional athletes make, as a rule, poor risks, giants are notoriously short lived, and excessively tall men often show a slender physique and deficient vitality.

Family History.—In English companies inquiry is usually made to cover only the immediate family, but in American companies it also includes the grandparents, and frequently direct inquiry is made as to the history of hereditary disease in collaterals. To the writer the larger scope of inquiry seems the wiser, and certainly in practical insurance work frequently develops

information of an important nature. In any case inquiry is always made in the form of a general question, such as, "Have any of your near relatives had consumption, insanity, gout, cancer, or other hereditary disease?" Many American companies now inquire directly as to the existence of tuberculosis or other pulmonary disease in members of the applicant's household, and particularly inquire as to any death from pulmonary disease occurring within a stated time in the household. During his service as a medical director the author used the following form of inquiry:

IN REPORTING FAMILY HISTORY STATE

So far as you know, what is the Age and present State of Health of each of the persons now living. What was the Age at Death, Cause of Death, of each of them, if Deceased? In giving the Cause of Death, avoid all Indefinite terms, such as "General Debility," "Change of Life," "Fever," "Exposure," etc. If the word Childbirth be used, how long after delivery did death occur, and were there any symptoms of disease of the Chest, such as Cough, Expectoration, etc. Where applicant cannot answer fully, he should explain why he does not know.

	LIVING.		DEAD.			
	AGE?	HEALTH? Be explicit.	AGE?	SPECIFIC CAUSE OF DEATH?	HOW LONG SICK? Be careful to state explicitly *duration* of fatal illness in every case.	HEALTH PREVIOUS TO FATAL ILLNESS?
Father						
Father's father .						
Father's mother .						
Mother						
Mother's father .						
Mother's mother .						
How many brothers						
How many sisters .						

Have *you or any of your blood relations* ever attempted suicide, or suffered from insanity, gout, rheumatism, epilepsy, consumption, cancer, apoplexy, or other hereditary disease?

Have any members of your immediate family (wife or children) suffered from consumption?

Are you intimately associated with any person having chronic cough?

The importance of a hereditary tendency to certain diseases cannot be doubted or undervalued, and the alternating tendency of many ailments must always be kept in mind. *Apoplexy* and *arteriosclerosis* are essentially one, and as alternatives *nephritis* and *heart disease* suggest themselves. Practically, equal value in the estimate of a risk must be attached to the *drug habit, alcoholism, epilepsy, hysteria, chorea,* and *criminal impulse as to insanity,* this being certainly true of three members of the group. The effects of *syphilis* are far reaching and important, but are not important in a life insurance history unless the stigmas of the inherited disease are evident to the examiner. Any inquiry along these lines is manifestly impossible.

Apoplexy.—Apoplexy offers one of the most striking examples in the whole range of hereditary diseases, the tendency in such families being to die in middle age; thus, the tainted applicant in such cases becomes an increasing hazard with every year of life. If such a history affect both parents, insurance is only possible under short endowments, and in relatively early life, and even when one parent has died in middle age of the disease a specially careful examination of the heart and bloodvessels is necessary. Risks showing any syphilitic, gouty, or rheumatic taint are particularly dangerous.[1]

Cancer.—In spite of the views so often expressed in opposition to the hereditary nature of cancer, the average practising physician and medical officers of life insurance companies will insist upon the affirmative of the proposition. The liability is undoubtedly greater upon the female than upon the male side, but affects both male and female lives.

Rheumatism.—This condition is often hereditary, directly connected with heart disease, particularly such as causes death in early life, and on life insurance blanks is frequently related to tuberculosis in the family history.

Diabetes.—The hereditary nature of diabetes is undoubted, and affects the rating of the risk much as does apoplexy.

Hæmophilia.—Owing to the peculiar atavistic transmission in these cases, the males of a tainted family are bad risks; the females suffer comparatively seldom from the disease, although passing it on to their male issue. Most deaths occur in childhood, but this does not affect the fact that such individuals of whatever age are uninsurable under ordinary policies.

Gout.—Gout and its alternatives, including certain forms of diabetes, is strikingly hereditary, and should be considered with apoplexy, arteriosclerosis, nephritis, and heart disease.

Tuberculosis.—That tuberculous infection occurs after and not before birth is an undoubted fact subject to few exceptions. The opportunities for acquiring the disease when it exists in family members are manifold. The children born into tuberculous families seem to possess tissues peculiarly vulnerable, and often show the delicacy of physique and deficiency in chest capacity associated with a pre-tuberculous state. Add to this the fact that they are especially liable to adenoid growths obstructing the nasopharynx, limiting the respiratory movements, and leading to chest deformities, and we have yet another reason for regarding with suspicion applicants of tainted stock. Yet another reason appears in the especial vulnerability of such persons to acute infectious diseases.

[1] The writer has reported a case in which every member of the family died of apoplexy, heart disease, or nephritis, with the exception of one brother, whose history is unknown. Out of eight members, only two reached the fifties.

At all events, applicants for life insurance possessing a family history of tuberculosis furnish a higher mortality than other lives, although the remaining policy holders show a higher mortality from the same cause than would appear if they had in every instance given a truthful and complete report.

The tendency to suppress vital facts is greater in connection with tuberculosis than in any other ailment except insanity. This is sometimes the result of a certain family pride, at other times possibly due to ignorance of actual conditions, and in yet others to the fear of jeopardizing their insurability. In estimating the importance of a family history of tuberculosis many elements must be considered, but in general it may be said that an exceptional physique and an attained age of thirty or thirty-five years goes far to counteract the family tendency. An applicant's liability to tuberculosis varies inversely as the ratio of healthy to infected family members.

The Degree of Relationship.—It is probable that from a practical standpoint there is little difference between the effect of parental disease and that of brothers and sisters in the family history, but ordinarily more weight is attached to the death of a parent, and especially to that of a mother, than to deaths in brothers and sisters. In this connection the matter of physical resemblance of the applicant to affected family members is undoubtedly important, hence the question covering this point ordinarily asked of American companies. Another point but little considered is the question as to whether either parent or other member of the family was suffering from the disease at the time of the applicant's birth or during his childhood.

Again, referring to the physique of such cases, *the writer does not hesitate to affirm that an enormous number of supposedly sound lightweight risks are really victims of latent or even incipient active tuberculosis,* and he further believes that although an exceptional physique goes far to neutralize a bad family history, it is not safe to assume tainted risks at early ages, or in the presence of unfavorable environment or association, even although the outward appearance is unusually favorable.

Long-lived Families and Short-lived Families.—Nothing is more interesting in connection with the study of hereditary tendency than the unquestionable fact that certain families tend to live long, resist acute disease, and long endure chronic ailments. On the other hand, every physician or life insurance officer is constantly meeting instances in which the opposite tendency is manifest, the general mortality figures being large for early ages, and resistance to both acute and chronic disease evidently far below the average. The former group not only makes the best life insurance risks, but may often be accepted under conditions which would make such action impossible in the case of even the average applicant.

Requirements of the Home Office.—All insurance companies desire that information as to the health of surviving family members and the cause of death or duration of illness in those deceased be full, specific, and concise, and that the state of health previous to the last illness be carefully investigated. Commonly used terms, such as "decline," "chill and fever," "malaria," "marasmus," "grief," "fever," "chronic bronchitis," and, above all, "*don't know*," are the bane of the medical director. In the rating of a risk most of these are assumed to cover tuberculosis or other hereditary ailment which the applicant is anxious to suppress, and it is consequently no less important for the insured than for the company that the examiner should conform to the requirements previously noted.

Matters of Importance in Relation to the Elimination of Tuberculosis and Heart Disease as Causes of Early Mortality.—No one at the present day will deny the necessity for and great benefit resulting from the medical examination of applicants for life insurance, but that these are as effective as they should be is conclusively disproved by all mortality statistics relating to deaths in the early policy years, which show an extraordinary number of deaths ascribed to diseases essentially chronic in their nature.

Deaths from heart disease should but rarely appear within five years of entrance, and during the first two years there should be but a trivial mortality from tuberculosis. As a matter of fact, both conditions cause heavy losses during the aforesaid terms. The writer has quoted in another volume[1] a number of cases of heart disease presenting the clearest possible clinical evidence, yet overlooked by insurance examiners, and granted insurance upon the plans applied for.

The explanation of this deplorable state of affairs depends chiefly upon three factors: First, *that modern diagnostic procedures are only to a limited extent represented upon the blanks of life insurance companies*, which nevertheless oftentimes obscure the chief essential (a thoroughgoing physical examination), through a multiplicity of questions. It is, of course, evident that the elaborate methods of the specialist and laboratory worker cannot be used under present conditions, both because of the time consumed in their application, and the fact that examinations must, in most instances, be made by busy general practitioners, but better blanks should be used. Second, the fact *that owing to the bitter competition existing in the past, particularly in the case of American companies, the agency department has been dominant, and the effort to secure new business has in many instances vitiated the work and crippled the function of the medical department.* In many companies doubtful applications are finally passed upon by a board or committee only in part composed of medical officers of the company, and in some instances so constituted as to place the latter in a hopeless minority. In one instance known to the writer the committee was composed of the *medical director, the president of the company, and the actuary*, and in the absence of the president the *superintendent of agencies* acted in his place. The bad result of such an absurd organization can hardly be doubted. *A third important factor tending to vitiate insurance selection results from the vicious system so often maintained in connection with the appointment and use of medical examiners.* By constant pressure and the plea that immediate attention must be given new applicants the agent in most instances multiplies examiners, is often allowed the chief part in their selection, and very naturally inclines to use the most pliant and least exacting physician. Only in the case of a very few American companies is a proper method pursued.

Finally, one must admit the carelessness of the examiner. His sins, both of omission and commission, are many, sometimes merely vexatious to agent and medical director, at others damaging and oftentimes inexcusable. In this respect, however, examiners are unquestionably improving, and in general are faithful and conscientious servants of the companies they represent, doing important work for a small fee. *If the American companies themselves would strive more energetically to emphasize the overwhelming impor-*

[1] *The Examination for Life Insurance*, second edition, p. 184.

tance of physical examination and make it absolutely clear, both by word and deed, that the companies want only first-class lives for ordinary policy forms, they could largely eliminate the present unfavorable factors and make an immense saving in mortality.

As illustrating the slackness of insurance requirements, one may cite the general failure to demand a careful preparation of the field of examination, viz., the chest. The author has been examined and passed for life insurance in two instances without being requested to do more than open the vest, and American companies very frequently fail to insist upon the proper removal or arrangement of clothing. Hence the frequency with which apical tuberculosis is overlooked may in a large part be chargeable to the fact that the apices in many instances are not examined at all. In the case of the heart, an examination is often worthless unless both the sitting and recumbent postures are made use of and all transmission and maximum intensity points examined. In the last three years half a dozen cases of mitral insufficiency have fallen under the writer's observation in which a murmur was clearly audible at the apex when the patient was lying down, inaudible when standing, save at the terminal transmission point of such murmurs at the left scapular angle. All of these cases, had they chosen to suppress subjective symptoms, would probably have received insurance policies. *Another frequent source of error is the failure to insist upon a normal tone and intensity in the heart and breath sounds,* this failure resulting very largely from the lack of training in this particular and the tendency to search primarily for murmurs rather than to prove normal conditions. It is self-evident that *male applicants should either strip to the waist or remove the clothing above that line, except the under vest,* which may and should be so shifted as to permit a view of the chest in every part.

Examinations should always be made in a quiet place, yet many of them are carried out in a busy workshop or noisy office. *The effects of stethoscopic pressure* should also be borne in mind by the examiner, as deep pressure tends to increase the intensity of any existing blowing murmur and diminish that of the vibratory murmur of stenosis. *Systematic tangential inspection of the chest and a proper valuation of accentuation and tone* would have made impossible the acceptance of several insured cases of aneurism which have come under the writer's observation. There is no material waste of time if a proper examination of the chest is made in a systematic manner, five minutes being ample for the inspection, auscultation, palpation, and percussion of all important areas.

It may be permissible to remind the examining physician of the fact that:

(*a*) Heart sounds should be normal in accentuation, tone, and time, and all murmurs absent, before any person applying for ordinary policy forms is recommended.

(*b*) That accidental murmurs due to excitement are common, and that hasty inferences as to pathological changes based upon an excited heart action are entirely worthless, involve a serious injustice to the applicant and demand repeated examinations.

(*c*) That every murmur should be timed by the carotid pulse, and not by the radial.

(*d*) That doubling or reduplication of the heart sounds calls for postponement and reëxamination even in the absence of other signs. Such symptoms are especially important in the case of middle-aged applicants.

(*e*) Arhythmia falls under the same head.

(*f*) The effect of exercise is often a clarifying factor.

(*g*) The persistent absence or marked diminution of a normal sound in its proper area is often of greater importance, although of the same general significance as a valvular murmur.

(*h*) The question of abnormal pulsation as relating to the apex beat, the region of the manubrium, the epigastrium, and the peripheral arteries should always be determined.

(*i*) It is impossible for any clinician or examiner to invariably detect cardiac lesions, but errors will seldom occur if the proper value is given to heart sounds, tone, and accentuation, and the ordinary procedure systematically followed.

The Pulse.—Decidedly rigid arteries are certainly abnormal if they appear before the age of sixty, although lesser degrees of sclerosis may be anticipated in most instances a few years earlier. Up to within a few years this enormously important factor in middle age mortality received little attention from life insurance officers, and even now rejections because of arteriosclerosis are relatively rare. The same man who would reject an applicant whose family history showed two or three deaths from apoplexy would pass another whose arteries were an almost absolute guarantee of early death, from that or an associated cause.

In taking the pulse for life insurance purposes both radials should be examined simultaneously; greater attention should be given to tension and actual sclerotic changes, which are even more important than arhythmia, tachycardia, or bradycardia, and the quality of the two pulses in strength and their coincidence in time be carefully noted. *A persistent high tension pulse is usually an important matter for investigation, although allowance should be made for the slight rise which* follows a heavy meal or that which is associated with the excitable and rapid insurance heart.

A pulse that runs above 85 should always demand an especially careful inspection of the lung apices and the use of the thermometer; a persistently high pulse is a bar to the ordinary form of insurance. The examiner should have in mind in such cases, aside from tuberculosis, neurasthenia or organic heart disease, the overuse of tobacco, physical exhaustion, and nervous overstrain. *A slow pulse* is in most instances distinctly pathological, and suggests a careful investigation of the heart and bloodvessels and inquiry as to a recent severe illness, inasmuch as it may follow acute infectious diseases.

Pulmonary Tuberculosis.—The evidence of improper selection is abundantly proved by the insurance mortality from this disease, which costs American life insurance companies nearly or quite $50,000,000 each year. Despite this fact, the companies generally have not been active in the campaign now being waged against tuberculosis, although self-interest alone would justify their coöperation or even the formation of an independent organization for the special purpose of aiding in the elimination of the scourge. It is particularly vicious in its effect upon the insurer, because of the tendency to early death, which means to insurance companies the payment of large sums to the beneficiaries of a group of policy holders who have paid in but little.

To the writer the apathy of the companies in this connection is incomprehensible, and no better proof can be adduced than the fact that up to the

time that the writer's book on *Life Insurance Examination* was published in 1900 hardly an insurance company in the United States demanded the use of the clinical thermometer, and even now such a requirement is omitted from many insurance blanks. When we consider that in one great company 18 per cent. of the deaths occurring in policy holders between twenty and forty years of age occurred *during the first two years* of insurance, this omission of an all important clinical feature seems unpardonable.

These deaths occurred among a presumably carefully selected body of policy holders, men selected upon the basis of a physical examination, reasonably good family history, and of an attained age supposedly removing them from the period of marked incidence. Under these circumstances, if the methods of selection were really ideal, the mortality of the first two years should have been purely nominal, not exceeding 2 per cent. of the total deaths from tuberculosis now occurring during the first year of insurance.

It is evident that life insurance companies are constantly accepting men in the active stages of tuberculosis, and in many instances these belong to the lightweight class. The following conclusions previously formulated by the writer seems therefore justifiable:

1. The present requirements of a majority of our insurance companies and the usual methods of insurance examiners are not sufficiently exacting to exclude persons suffering from incipient or arrested tuberculosis.

2. Improper preparation of the patient is a fertile source of error, and should be covered by specific instructions and direct inquiry, as is now done in but few instances.

3. Light weight in an applicant should lead to a careful scrutiny in every case, and suggests an afternoon appointment for temperature determination. Many accepted as sound liggtweights are actually cases of incipient or arrested tuberculosis.

4. Heavyweights cannot be accepted at their face value.

5. Recent loss of weight is suggestive and important. It is important that the "best" weight should be stated. No blank known to the writer contains the latter inquiry.

6. Hoarseness should arouse suspicion, and be met by postponement until recovery.

7. The routine determination of the body temperature is extremely important, and its present neglect inexplicable.

8. The physical signs of tuberculosis are obscure, and require skill and judgment, both in their detection and the weighing of their importance. The proper attitude, viz., demonstration of the normal, greatly simplifies matters.

9. Hence a knowledge of the normal chest is all important.

10. Unilateral hyperresonance is as important as unilateral dulness, and absence of the normal breath sounds no less significant than the presence of abnormal sounds.

11. Broadly speaking, the examiner must rely upon auscultation more than on percussion. No one sign available to the insurance examiner is pathognomonic, and hasty conclusions are deplorable and disastrous.

12. The tuberculin reaction and the demonstration of tubercle bacilli in sputum are impracticable measures, save in the case of substandard lives.

13. Greater stress should be laid upon the question of direct infection, and specific questions in relation to environment should be inserted in every medical blank.

14. Kroning's method of apex percussion should be more widely known to insurance examiners, as readily indicating apex retraction due to present or past disease.

INSURANCE OF SUBSTANDARD LIVES.

The Standard Life.—A standard life is one that offers a reasonable prospect of reaching an *advanced age*, not merely an individual life which seems likely to attain its *tabular expectancy*. The latter represents the mean after-lifetime of any group of supposedly long-lived men of the same age, the long-lived members being balanced against those who fall by the way. Any individual whose probable after-lifetime is only the number of years represented by the average of a thousand men of the same age would be an extra hazardous risk.

Difficulties Incident to Substandard Rating.—It would seem most desirable that all persons should have an opportunity to secure protection for their families through life insurance, and that this desideratum might be reached with justice to all through a thoroughgoing investigation of the statistical data available after many years of life insurance experience.

Inasmuch, however, as *such insurance to be ideal must be founded upon a just premium, absolute safety for the company, and a system of grouping which relieves the good risks from the enforced burden entailed by the expense of carrying bad ones*, the problem has proved so complex that up to the present time no perfect solution has been attained. This is due to the remarkable fact that up to the present time no adequate collective investigation has been carried out by the British companies, although these have for years dealt with substandard lives, each in its own way and according to the individual ideas of the chief medical officers and actuaries of the companies. In the United States the insurance of invalid lives has been frowned upon by the great body of insurers, and only within the past few years have a few important companies attempted to carry out substandard plans, either exclusively or in connection with the more usual method.

One thing would seem to be proved, namely, that the matter of *safety* to the company is readily taken care of. The problem of *equitable* rating has not been attained in most instances, as the writer knows from personal observation of patients carrying policies of the substandard type, some of whom might readily have been accepted with slight or no addition, but were rated so high as to make them assume the burden of other risks of a definitely dangerous type.

Apart from the factors previously mentioned, it would seem that, inasmuch as prognosis is the most difficult and the least studied of all medical problems, so far as the general practitioner is concerned, and inasmuch as the insurance companies must depend upon the presentation of vital facts by men for the most part not specially trained in this peculiar and special line, absolute accuracy in classification and hence equity in rating must remain a desired but unattainable achievement. The apathy of the British companies in this connection is disappointing, and it would seem that an early effort should be made to carefully collect the enormous data available, set aside the groups representing impairment of definite kinds and degree, and work out the after-lifetime in such groups, thus obtaining the basis for just and proper rating without excessive profit. Such an investigation would also quite certainly

result in showing that certain classes were at the present time decidedly underrated.

Another investigation should comprise the study of the after-lifetime of rejected risks, a matter presenting no insuperable difficulties for either British or American companies, and likely to prove of great value both to the ordinary life insurance companies and those doing a substandard business.

Methods of Substandard Rating.—Aside from certain individual schemes, the methods at present in vogue are such as to cover, as adequately as rough and insufficient data will permit, the four chief sources of increased hazard in life insurance acceptances, viz.: (1) Unfavorable family history. (2) Unfortunate environment, habits, and occupation. (3) Past diseases threatening recurrence or inviting other ailments. (4) Existing organic diseases or actual lack of vitality.

It is evident that in all cases the insurer deals with (*a*) applicants in whom the risk increases with each year of insurance, "increasing hazards;" (*b*) those of diminishing risk with the lapse of years, "decreasing hazards;" and (*c*) those in whom added risk is a constant factor, "permanent hazards."

To meet these varied conditions the company may adopt any one of four plans: (1) Merely increase the premium; (2) advance the age; (3) place such a lien upon a policy as makes a certain amount deductible if death occurs within a stated period, the sum to be subtracted steadily diminishing as the policy ages; and (4) issue endowment policies to cover slight additional risk, particularly if the element of risk involved be of the increasing variety. This last method really involves almost exclusively the time limitation of the risk.

The following table will make clear certain methods of rating:

ANNUAL EXTRA PREMIUM PER CENT. (UNLOADED) INSURANCE, $1000.

AGE AT ENTRY.	EXPECTATION OF LIFE.	ONE-FOURTH OF ONE PER CENT.		ONE-HALF OF ONE PER CENT.		THREE-FOURTHS OF ONE PER CENT.		ONE PER CENT.	
		Initial Deduction.	Rated-up Age.	Initial Deduction.	Rated-up Age.	Initial Deduction.	Rated-up Age.	Initial Deduction.	Rated-up Age.
20	42	$375	27¾	$610	32½	$755	36¼	$860	39¼
25	38	360	30½	610	34½	755	38	860	40¾
30	35	330	34¼	550	37¾	710	40½	810	43
35	31	300	38¼	510	41	660	43½	755	45¾
40	27	265	42½	460	44¾	600	46¾	715	48½
45	24	220	47	390	48¾	510	50½	610	52
50	20	185	57½	330	53	450	54¼	550	55½
55	17	150	56	270	57	380	58	470	58¾
60	14	115	60¾	210	61½	300	62¼	380	62¾

NOTE.—The table is read as follows: A net extra premium of one-half of one per cent. at age thirty is equivalent to an addition of seven years and nine months to the age, and is equal to a deduction from the sum assured, commencing at $550 and diminishing by $15.70, or one thirty-fifth part, for each year survived until the original expectation of life at age thirty (thirty-five years) has been outlived. —*From Pollock and Chisholm (modified).* (*The Examination for Life Insurance*, Greene.)

The following table, prepared by Mr. R. M. Moore for Dr. Hingston Fox, shows very clearly the advantage gained by the substitution of the twenty-payment life or thirty-year endowment for the straight-life policy:[1]

Approximate Loss Per Cent. to Company on Death at Various Years After Entry.

Male Life, Age Twenty-one at Entry.	Years in Force—*i. e.*, Age of Policy.								
	1	6	9	16	21	26	31	36	40
Ordinary whole life policy . .	98	89	77	63	47	28	5	+22	+47
Ordinary whole life policy, advanced seven years . . .	98	86	72	56	36	13	+14	+47	+78
Ordinary whole life with a deduction equivalent to seven years' advance	82	75	65	53	39	22	1	+24	+47
"Limited payments" (20), advanced three years . . .	97	82	64	43	21	6	+12	+33	+52
Endowment (thirty years) — *i. e.*, terminating at age fifty	97	82	63	41	15	+16	+37 (29 yrs.)		

Only the net premiums are taken account of, and no office loading or bonus is allowed for; interest is at 3½ per cent. The + sign signifies gain.

These tables are self-explanatory, but it will be noted that in every case the actual rating involves the personal opinion of the medical man as to the prognosis in the individual case.

Extra Ratings as Imposed by Certain British Companies.—As examples of the methods pursued, the following list of ratings may prove useful, but it must be borne in mind by the reader that great variations occur in the rating as made by different insuring companies.

Use of Alcohol.—Definite ratings seem to be unobtainable. All recognize that the hard drinker is uninsurable, that graduates of so-called "cures" show a tremendously increased mortality, and that the reformed should not be accepted for several years following the cessation of their use of liquors.

Asthma.—Recent attacks mean rejection; slight attacks in youth need not affect the adult applicant if the heart and lungs are normal. *Remote* attacks in older persons should limit the applicant to an endowment terminating not later than the age of sixty. Actual asthmatics could hardly be considered as promising to live more than half of the expected normal term.

Nephritis.—The discussion of the insurability, at ordinary rates, of such persons as carry a persistent trace of albumin with an occasional cast has taken up much time in the discussions of medical societies, and the relation of slight traces of albumin and of the occasional cast to the present health and after-lifetime of the individual remains apparently an unsolvable problem as related to life insurance. *Such discussions are almost wholly futile, inasmuch as practical experience shows that no company can insure at ordinary rates applicants reported as suffering from albuminuria of the renal type, even although this be slight and intermittent.* The deadly significance of insurance statistics bearing upon this head is unmistakable, and the figures

[1] *Transactions of the Life Assurance Medical Officers' Association. The Medical Examiner*, August, 1895, p. 176.

are not to be shaken. Every applicant should have a fair chance in the way of reëxamination, as unquestionable error occasionally occurs because of lack of skill on the part of certain examiners, yet these incidents are few in comparison with the many cases in which an albuminuria or indeed an established nephritis is overlooked.

Blood pressure determination should become a part of the routine examination of risks for life insurance, and results should go far in determining the question of rating of actual cases. "Functional," "psychic," and "intermittent" albuminuria are of importance to the practitioner, but their discussion in relation to life insurance is academic. In especially favorable cases of albuminuria (without markedly increased tension, bad habits, or excessive weight, and lacking casts or unfortunate family history) English companies occasionally grant an endowment policy with an addition of ten years, terminating at the age of fifty or thereabout. The hazard is an increasing one, and lends itself less happily to the lien plan which is sometimes applied. Established nephritis of the ordinary type is seldom rated at all.

Aortic Regurgitation.—In exceptional instances a few English Companies accept with heavy extras. Young adults are charged from twenty-five to thirty years addition; middle-aged applicants as much as $300 per thousand of insurance on a ten payment basis.

Aortic Stenosis.—With well-marked primary and secondary symptoms this is usually regarded as uninsurable, although many cases presenting aortic systolic *murmurs* are insured at considerably lower rates than would be granted to cases of regurgitation.

Arteriosclerosis.—Endowments are granted terminating at fifty with or without extra according to family history and grade of disease. Markedly sclerotic or symptom producing cases, those with gout or rheumatism, or those of exceptionally bad family history, are rejected.

Appendicitis.—The English companies rate up from five to twenty-five years cases of appendicitis in which the appendix has not been removed. The risk is considered exceptionally great in women who have suffered from a previous attack, because of the liability to recurrence during pregnancy.

Blindness.—Complete blindness is covered by an addition of about 10 per cent. The cause must of course be taken into consideration, as this extra is intended to cover the accident hazard only.

Cancer.—Those of tainted family history may, if under forty, receive an endowment terminating within ten or fifteen years; if over forty, will be heavily rated up or rejected altogether if more than one death from cancer has occurred in the family, and even in the case of one death if this be that of the mother and the applicant a female.

Deafness.—Complete deafness is usually covered by an addition of not less than five shillings per cent. (*i. e.*, per £100 of insurance), this being intended to cover additional risk of accident only. As in the case of blindness, the cause must be carefully considered.

Diabetes.—With a decided family taint applicants under forty are rated up five years or more, and over forty from seven to ten years. Actual diabetics are not accepted.

Dyspepsia.—The wide diversity of dyspeptic conditions and their relation to other diseased states make it impossible to establish fixed rules for acceptance or extra rating.

Drug Habit.—Save in most exceptional cases, victims of the drug habit are regarded as uninsurable, even after apparent cure.

Epilepsy.—If absolutely free from hereditary taint and from seizures within ten years, these cases are occasionally granted insurance under varying extras.

Emphysema.—If associated from frequent attacks of bronchitis, persistent cough, or occurring in poor persons, the condition demands rejection; otherwise endowment with or without an extra.

Fatty Heart.—This is not insurable.

Mitral Disease.—Exceptionally favorable cases under forty years of age, free from dyspnœa on exertion, well circumstanced, causative factors remote, etc.—five to fifteen years addition or less if endowment terminating at fifty be taken.

Pott's Disease.—From ten to fifteen years' immunity from all symptoms, an exceptional state of health, and clean family history render certain slight cases insurable, but always with a heavy extra and best under endowment.

Pregnancy.—Pregnant women are accepted by some offices under an addition varying from $2.50 to $16.00 per $1000 of insurance. Primiparæ and those women under twenty are rated higher than multiparæ unless the latter have borne an excessive number of children. A history of excessive hemorrhage, convulsions, contracted pelvis, frequent miscarriages, and the like demand heavy rating or even rejection.

Tuberculosis.—Actual cases of tuberculosis are uninsurable. Cases of arrested tuberculosis might exceptionally be taken under heavy additions if the age of forty has been reached, all symptoms absent for at least ten years, the physique and weight exceptionally good, and the family history clean and *indicative of inherited resistance to disease.* A tainted family history is difficult to deal with.

One set of rules proposed by Pollock and Chisholm is quoted by the writer in another volume (*Examination for Life Insurance*).

Dr. F. de Havilland Hall proposes the following classification: "Degrees of Heredity." (*a*) Implication of one brother or sister or one collateral. (*b*) Implication of brothers and sisters; many collaterals with sexual limitation; the father's heredity alone. (*c*) Implication of grandparents, father, with one other of the children; the implication of many brothers and sisters; the mother's heredity alone. (*d*) Father, with many members of the family; mother, with other members of the family; grandparents and parents; double heredity. He then uses four age periods: (1) Under twenty-five, (2) between twenty-five and thirty-five, (3) thirty-five to forty-five, and (4) beyond forty-five. Under the first age period all tainted applicants are rejected. Under the second age period Class (*a*) receives ordinary rating if physique and environment are good and if the applicant is in comfortable circumstances. Classes (*b*) and (*c*) are accepted under the same restrictions, with additions running to five or seven years. Third period. Class (*a*) at ordinary rates. Class (*b*) at three years' addition. Class (*c*) with five years' addition. Fourth period (over forty-five years of age). Classes (*a*), (*b*), and (*c*) at ordinary rates. Class (*d*) in exceptional, carefully selected cases at ordinary rates, but usually with an extra.

Varicose Veins.—If extremely painful or leading to ulceration, past or present, persons with these are rejected or heavily loaded.

The foregoing rules of British selection are merely illustrative, and there is a deplorable and most significant variation in the action of the various offices, but in almost every instance the selection is safe and profitable from the standpoint of the insurer.

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